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SOME THOUGHTS ON PRECEDENT *

MARTIN F. ENGMAN, M.D.
ST. LOUIS

To preside over this body which represents the most eminent in American dermatology is indeed an honor and one to which laudable ambition should aspire. I, no different in this respect from my peers, feel highly gratified that this office should have come to me and I wish to express to you, my colleagues, my gratitude and high appreciation. To preside over the annual convention of such an assemblage as that represented by the American Dermatological Association is not a hollow honor but carries with it responsibilities; responsibilities which nag one for many months before the day of culmination or execution. One of these, the most weighty, the one which has borne most heavily on this presidential crown, is the annual address.

In reading the addresses delivered by your presidents for many years back, it appears that of the subjects I might select, all have been exhausted: the history of this Association, its past and future have been well discussed; the journal—our pride—its history, its editors and shortcomings have been well discussed; the history of dermatology has been well discussed; so what is left for me but the broad field of dermatology?

I am sure there is nothing so interesting to dermatologists as skin diseases and their discussion, with the possible exception of golf, to some of our older and heavier members.

The presidential address is not limited as to time; the hammer of the presiding officer does not abruptly stop its flow; it may, like Tennyson's brook, babble on forever. And there is no prescribed limit to its scope; one may hurdle pedantic fences, hoary with precedent, and gambol in the glad sunshine of this liberty.

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* Presidential address read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April 22-24, 1920.

* Studies, reports and observations from the Dermatological Department of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, St. Louis, Mo., U. S. A., Service of Drs. M. F. Engman and W. H. Mook.

The presidential address seems to act, at times, like one of those potent potions concocted during the middle ages to clear the system of humors. It seems to act in this way on the dermatologic system; it drives dermatologic humors, that have been stored up for years, to the surface.

With the glad feeling of liberty which you have thrust upon me in meeting assembled, I will open the gates to this large dermatologic field and will playfully gambol about in its patches of shade and sunshine; but I promise you I will return home long before the lunch bell rings. Whether you will receive proper invigoration by my exercise will remain a question.

Those who have given years of study to a special subject must finally come to the mental condition of those ancient Greek philosophers who, realizing the fallibility of all human knowledge, saw the impossibility of demonstrating truth even though truth be evident. One feels almost like Arcesilaus who, denying both intellectual and sensuous knowledge, publicly avowed that he knew nothing, not even his own ignorance. Experimentation and verification have been the two criteria of truth in its modern demonstration. To medicine these attributes have been as the wings of progress.

We who have been engrossed in the study of skin diseases for a quarter of a century or more must, if we have normal minds, realize our ignorance: how little we can possibly add to the chaos of things to be known, in the short space of a lifetime! To the novice the textbook and the printed page is as the chapter of Genesis was to the theologians of the middle ages—almost divine truth. But as the mind matures, considers and dwells on the fallibility of human knowledge, inquiry is awakened and often heresy results. Epicurus rightly taught that truth can never be determined by pure reason. The scientific trend of the modern mind demands and seeks experimentation for the verification of truth. This is not the trend of all modern minds, not the nature of all modern minds; the majority are probably pre-Platonic and do not reason from observed details to generalities.

Medical literature, especially dermatologic literature, is still carrying along on its many pages folk-lore, legendary data, obsolete theories and vague fancies, indelibly impressed on those pages by precedent. The same force—a virile potent force it is—has engrafted and impressed on the life of all ages and peoples, fallacies born of legend that centuries and centuries have nurtured.

The study of a science should not only be the acquirement of knowledge that has accumulated in the past, but inquiry into the truth of that knowledge and the demand of verification; and, if that is not satisfactory or sufficient for mental quietude, investigation anew to determine truth, is demanded. But how many of us assembled here have time to

seek this goal? Our branch of science has not received that gift of the gods—endowments. We, the devotees, plod along the weary path of bread-earners, chained to the necessity of earning a livelihood, while we yearningly look into the unexplored fields of research as we pass along. Yet many here, and many others who have sat in this assemblage have, in moments of recess, delved into these alluring places and have blazed trails to many truths.

All fields of research are full of stubble, weeds and thistles, which from their very nature must be removed before truth can be found, yet knowing this we turn our novices into these fields, the books and literature on these subjects guiding them into false snares: guides which we, the older ones, have found false or inaccurate in many ways. In other words, we pass to our students through books, lectures and magazines, observations or data that have clung to our literature for many decades and which have not stood the test of time and verification. The history of a disease and its literary evolution is interesting and important; but why continue to place among the etiologic factors, for instance, data that at the present time bear no relationship to the disease in question, other than as a matter of history; and under "treatment" the results of folk-lore, legends and medical deductions based on false premises? Ideas and thoughts that have died years and years ago still haunt the pages of our literature. These ghosts stand out gauntly on many pages—emblems of precedent. Precedent is ever with us, menacing to some, acceptable and comforting to others; the greatest handicap to progress, the check to inquiry, the bugbear of the ages, the cloud which so frequently obscures truth. Khaliff Ali, the son-in-law of Mohammed, remarked that "in the course of my long life, I have often observed that men are more like the times they live in than they are like their fathers." We live in an age of inquiry and investigation and we, like the times in which we live, are investigators in a modest way. Inquiry and investigation have always been the undoing of precedent; they have riddled and destroyed false theories and beliefs that have held men's thoughts in iron chains for ages.

Realizing that precedent was the greatest handicap to dermatologic progress, and not being very reverential, some curious thoughts and heresies have come to me as a result of inquiry, sometimes verified by experiment, sometimes not. The same thoughts have no doubt occurred to others. Among these inquiries I have often thought of diet in skin diseases—why is meat and the nitrogen partition such a dreaded thing —why the cry in all diet lists—meat—beware of meat? Since Emil Fisher gave us those eighteen or twenty "building stones" of the protein molecule to play with, we have built many theories and have juggled these building stones about joyfully. Nature, it seems, can play havoc and cause many curious eruptions with these "stones." She can build

subtle molecules which may slip by the best regulated and most careful intestine cells and cause all kinds of trouble. We do not exactly know the physical appearances of these troubles, but we feel that we have an intuitive knowledge of them; therefore, in order to be positive that such devilish juggling of building stones does not occur again or continue, we prevent the entrance of meat into the patient's body. We fear meat just as the ancients did, but we are not so discriminating as they were; in certain conditions they allowed only the food of animals that fed on certain shrubs or trees. Meat from old animals was said by them to produce foul and burning humors.

When man first became conscious that he was man, he was probably hanging from the limb of a tree with one foot, while he grasped a branch with another, and cracked nuts or ate fruit. He was a vegetarian. When the chilling blasts of the last glacial period drove him hungry and starving, south into the tropics, even there the cold had killed his vegetable foods; the vegetarian was forced to kill and eat his kind or another kind in order to live. He then became a meat eating animal. As he took his first bite of meat, did he begin feeding himself for kidney diseases, joint diseases and skin diseases? Did the serpent hand a tenderloin steak to Eve instead of an apple? Is there a mistake in the old Chaldean legend? Was this mastication of meat the birth of sin, disease and death? If not, why and on what ground of investigation and experimentation is red meat, animal protein, so interdicted in diet lists. Man has eaten meat for at least 240,000 years as estimated by learned anthropologists and ethnologists, and although many have died during that time, he, when not interdicted by his doctor or his purse or other circumstances, will still choose meat in preference to his anteglacial nuts.

Protein sensitization has come to our assistance and seems to be forming some order out of these chaotic ideas of meat diet. Focal infection has taken from the heterogeneous mass of diseases supposed to be due to protein diet, arthritis, rheumatism, certain forms of gout and certain skin eruptions. Haig's beautiful work on uric acid diathesis is one of the ghosts that still haunt the pages of medical books. The study of focal infections and protein sensitization are clarifying the cloudy obscurity of certain chronic kidney conditions. We must admit that learned and well thought out diet lists have been propounded for various diseases founded on precedent, to which the patient has been made to fit. So it is carried out today and will be tomorrow. The trend has been to make the patient fit the diet, and not the diet the patient. What a flood of light has been thrown into these dark recesses by the work of such men as Funk, Osborne, Mendel, McCollum, Goldberger and others. The chemical bodies contained in certain foods called "vitamines," so necessary to life's equilibrium, are probably the funda-

mentals of diet. How many diseases at present classified under obscure and numberless etiologic factors are due to unbalanced diets—diets in which a high protein intake is necessary, proteins or other foods taking with them those life and health giving, elusive chemical principles? How rapidly do the papulonecrotic tuberculids in children seem to disappear, together with the scrofulous glands under a diet rich in butter, cream, lamb and those foods known to contain growth vitamins! McCollum's book on the "Newer Knowledge of Nutrition" is an intelligent guide in this wilderness.

How many pathologic conditions are due to vitamin starvation, meat starvation, egg stuffing or milk inundation? What a great loss of energy is sustained in those cutaneous disorders in which almost the whole surface is inflamed and covered by scales with multiplied surfaces which increase evaporation and the dissipation of heat, as in the erythrodermas! How necessary, therefore, in these conditions is an increased intake of foods, nourishing and of high caloric value, such as alcohol, sugar and cream with meat and proteins for endurance and stability. How grateful to the patient is this increase of calories and how successful in keeping up the equilibrium for defense against intercurrent infections.

The intricate synthesis of lipoids and fats is still a physiologic problem, especially in dermatology with its Hebraic ideas about oily seborrhea. Is oily seborrhea due to an excessive intake of fat, or is it due to the small bacillus of Sabouraud? The Fucks-Hebra idea of seborrhea still stalks in our midst. Is it a disease; is it a dietetic disease? If a dietetic disease, on what evidence, except that furnished by precedent, is it classified as a dietetic disease? On what scientific evidence or verification or experimentation has this idea, as to its dietetic and hygienic origin, been established? The seborrheic state and its progeny—acne and the seborrheids—appear with those secondary sexual characters recognized as the dawn of puberty. The shiny nose of the high-school girl is as sure a sign of puberty as the little powder puff and silver vanity case. Some noses shine more than other noses, some skins ooze more oil than other skins, but by what standard or unit shall we pronounce disease? Shall we say the cause of this excessive cutaneous production of oil is the ingestion of fats, sugar, chocolate, candies and rich foods, because nature at that age demands such foods as butter and cream vitamins and those of high caloric value that can be easily burned? How do we know that acne vulgaris with the embryonic comedo is due to the rich food intake craved by youth? The microscope does not verify this old theory. It analyzes the acne lesion as one caused by the presence of a bacillus, always there just as a bacillus is always present in the tubercle of tuberculosis. Do chocolates, pancakes, pies, cake, sugar,

fats and candies cause such a lesion? Can such a theory be verified by our general knowledge of histopathology? Can we assert that diet might cause directly or indirectly a lesion such as acne? But we have lesions similar to those of acne, due to the presence of organisms in the lesions. This fact we can use as a clue for verification. Oily seborrhea and the comedo are the insignia of youth and the dreams of puberty. Seborrhea is a type, the representative of a strain, a family. How the poets paint these types; they see them undisturbed by precedent.

Dickens paints Mr. Chadband with wonderful truth. How oily he was, how he beamed and oozed oil! Mr. Chadband, we know, must have had acne vulgaris in his youth—he had the scars of it. Was his oiliness a disease or a part of Mr. Chadband's nature? Was it a part of him, just as much a part of him as his nose with its large pores and thickened yellow skin? It may be that Mr. Chadband ate too many stimulating vitamins in his youth. Who knows? But is it not more likely that Mr. Chadband was of a strain, the result of Mr. Chadband's progenitors? To such skins as that presented by Chadband, Darier wishes to apply the term "kerosis"—recognizing it as a type or strain of individual.

As Buckle has pointed out, environment and diet form racial types and consequently racial natures; therefore, back in the dark recesses of history may lie the cause of oily seborrhea, the fundamental condition that furnished the soil for those seborrheic diseases so well portrayed by Sabouraud. Besnier, Audry and Darier see with the poet's eye the type of man who oozes oil, has acne, yellow skin and stringy, greasy hair.

Precedent has been one of the strongest outposts against the advance of inquiry into diet. Diet is elusive and mysterious, yet through inquiry light is being brought to bear, through diet, on that mysterious condition of the skin so often fought over and so elusive—eczema. Through a knowledge of sensitization, types, strains of men, environmental conditions, trades, occupations, histopathology and experimentation the eczema of our teachers, the eczema of too much meat, the eczema of the diet of the century past proves to be a ghost, a phantom, wrapped in the mystery of precedent.

The exudative diathesis of Czerny is a living type, living and pathetic; with enlarged glands, bronchial cough, oozing, scaly skin—on through life suffering, exudative! How we have followed precedent in the treatment and elucidation of these cases, until the study of sensitization brought the light. What truth was there in the past ideas of diet in these cases when fats, proteins or mineral salts were excluded? Some of these cases are now known to be due to wheat sensitization; some to egg, some to pollen, and others to bacterial

sensitizations. How many young lives have been lost by intercurrent infections due to the lowered resistance of a restricted diet.

How interesting at the present time are all cases of so-called eczema, the solution of which means the employment of inquiry and investigation in each individual case, the flow of imagination, the pleasure of inductive reasoning, the joy of success. Life's work takes on a pleasanter phase and new vigor when one's own inductive powers can be used instead of the wise shake of the head with the printed diet list in the handling of acute, subacute or chronic eczema.

Soiling lotions, greasy salves, nauseous concoctions, starvation diets, quassia, gentian, alkalies, acids, arsenic may now be replaced by inductive reasoning, inquiry and investigation. How much longer will the ghost of eczema theories cling to our literature; how long the eczema diets of yesterday? How much longer will the urticarial lesions, the lesions of erythema multiforme, drug eruptions and others of this character be hung on the fibers of the vasomotor system? Histopathology has appeared to portray to us only a picture of morphology in the study of these eruptions, and it has been comforting to believe that somehow through the subtle influence of a "toxin" on the vasomotor system these eruptions occur; yet von Duhring, Phillipson and Gilchrist have told us of their purely inflammatory nature, of the wonderful biologic and chemical forces set in operation at the site of these lesions; however, we still take the comforting vasomotor view of all the eruptions of the erythema and urticarial groups.

Dermatology is a wonderful field for research and inquiry; a beautiful study and one that its devotees should love, for it contains so many wonderful things—things that fit into the very fundamentals of life. It is a constant source of inspiration. Its lesions, though on the surface of the body, are symbols which speak of deeper things, often of life's most obstinate and hidden problems; lesions significant often of trades, occupations, habits, customs, types, races, families, diseases lying deep in the system, dispositions, vanities, frivolities, physiologic periods; even flitting thought often leaves its impression as a blush or a lesion.

The skin and its digression from the normal is a study which should inspire one to employ all the forces of inductive reasoning, inquiry, investigation and experimentation in the search for truth—but truth shorn of precedent.

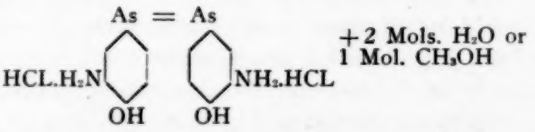
THE CHEMISTRY OF ARSPHENAMIN AND ITS RELATION TO TOXICITY *

GEORGE W. RAIZISS, M.D., AND A. PROSKOURIAKOFF, M.D.
PHILADELPHIA

In many cases reactions must be attributed to individual intolerance for the drug. Undoubtedly, when a number of patients receive arsphenamin of the same lot by the same method of administration and only one or two show reactions, it is safe to assume that they are due to an idiosyncrasy.

There are also numerous cases in which the technic of the intravenous administration is responsible for serious reactions. Schamberg, Kolmer and Raiziss [1] were the first to suggest that the cause of reactions can be attributed to impurities in the drug. "We are firmly convinced that the complex symptoms characterized by flushing, edema, etc., are due to the drug administered and not to extraneous causes."

This is the graphic formula of arsphenamin:



The analyses for arsenic, nitrogen and other elements in most of the samples correspond to the above formula with two molecules of water of crystallization. Ehrlich and Bertheim [2] thought that the compound crystallized with one molecule of methyl alcohol. Kober [3] called attention to the fact that there is no definite proof of the presence of two molecules of water of crystallization in arsphenamin. He is inclined to assume the presence of one molecule of methyl alcohol because arsphenamin usually is precipitated from solutions containing methyl alcohol.[4]

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* Read before the joint meeting of the Section on Pharmacology and Therapeutics and the Section on Dermatology at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

* This work was made possible by funds accruing from the dispensing of arsphenamin.

* From the Dermatological Research Laboratories.

1. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: Experimental and Clinical Studies of the Toxicity of Dioxydiamino-Arsenobenzol Dichlorhydrate, J. Cutan Dis. **35**:286, 1917.

2. Ehrlich, P., and Bertheim, A.: Ueber das salzsaure 3, 3-Diamino-4, 4-dioxyarsenobenzol und seine nächsten Verwandten, Ber. d. deutsch. chem. Gesellsch. **45**:756, 1912.

3. Kober, P. A.: Preparation of Arsphenamin, J. A. Chem. Soc. **41**:442, 1919.

4. The authors are at present engaged in the investigation of this question.

The comparatively rapid oxidation of arsphenamin when dissolved in water or organic solvents, the difficulty of obtaining it in crystalline form and other factors make the purification of the drug practically impossible.

A compound, which cannot be repeatedly crystallized or purified by other means, is apt to contain impurities. It is possible, therefore, that the cause of the reactions observed in patients receiving intravenous injections of arsphenamin lies in the impurities of the drug.

TABLE 1.—Results of Analysis of Various Compounds of Arsphenamin Prepared in Other Research Laboratories

Compound	Clinical and Animal Records	Percentage of Arsenic	Percentage of Nitrogen	$\frac{As}{N}$	Deviations from Theoretical, Percentage	Mg. of Oxygen Absorbed by 100 Mg. Arsphenamin	$\frac{Mg.\ As}{Mg.\ O}$	Deviations from Theoretical, Percentage
Theoretical for arsphenamin + CH_3OH	.....	31.85	5.95	5.35	...	13.47	2.34	
2551	Good	30.17	5.45	5.53	3.4	13.10	2.32	0.8
3695	Good	31.20	5.75	5.40	0.9	13.35	2.34	0.0
3695—Ra	Good	30.44	5.76	5.30	0.9	12.95	2.35	0.4
3252	Good	29.32	5.40	5.45	1.8	12.99	2.34	0.0
3735	Good	30.00	5.58	5.40	0.9	12.90	2.33	0.4
2859	Animal records unsatisfactory	30.50	5.65	5.40	0.9	12.90	2.37	1.3
3084	Animal records unsatisfactory	30.31	5.70	5.32	0.5	13.00	2.33	0.4
3181	Animal records unsatisfactory	29.30	5.45	5 37	0.5	12.80	2.30	1.7
3350	Animal records unsatisfactory	30.50	5.65	5.40	0.9	13.60	2.24	4.3
3454	Clinical records unsatisfactory	30.18	5.70	5.34	0.2	12.75	2.36	0.8
3492	Clinical records unsatisfactory	31.75	5.90	5.37	0.5	13.05	2.43	3.8
3462	Clinical records unsatisfactory	30.40	5.75	5.30	0.9	12.79	2.38	1.7

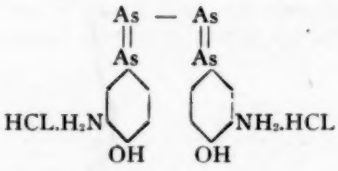
This and the following papers are devoted to the study of the chemical composition and the isolation of compounds which constitute the impurities in arsphenamin. The authors analyzed a considerable number of lots produced at the Dermatological Research Laboratories and other laboratories. The chemical composition of lots which proved to be particularly toxic for the experimental animal or produced severe reactions in patients were compared with the composition of those that were well tolerated. An attempt was made to establish a relationship between the purity of the compound and its toxicity.

This paper deals largely with arsenic and nitrogen contents and the degree of reduction of arsphenamin.

THE ARSENIC CONTENT OF ARSPHENAMIN

According to its chemical formula with either two molecules of water of crystallization or one molecule of methyl alcohol, arsphenamin

contains 31.6 per cent. and 31.85 per cent. of arsenic, respectively. A lower arsenic content would indicate moisture, methyl alcohol, ether or other organic solvents as the result of insufficient drying. Inorganic impurities, such as calcium or magnesium chlorid or salts of heavy metals also lower the percentage of arsenic. Higher arsenic content, on the other hand, may result from a loss of water or methyl alcohol of crystallization, by too vigorous drying, also by the presence of impurities such as polyarsenical compounds of the following formula:



Again, higher arsenic content may indicate the presence of arsenophenols or inorganic arsenical compounds.

TABLE 2.—Results of Analysis of Various Compounds of Arsphenamin Prepared in Other Laboratories

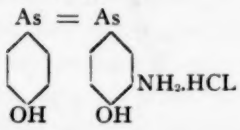
Compound	Percentage of Arsenic	Percentage of Nitrogen	As / N	Deviations from Theoretical, Percentage	Mg. of Oxygen Absorbed by 100 Mg. Arsphenamin	Mg. As / Mg. O	Deviations from Theoretical, Percentage
Theoretical for arsphenamin + CH_3OH	31.75	5.95	5.35	...	13.47	2.34	1.0
Arsphenamin from laboratory No. 3, sample A	31.44	5.74	5.51	3.0	13.20	2.38	1.7
Arsphenamin from laboratory No. 3, sample B	32.26	5.58	5.79	8.2	13.36	2.41	3.0
Arsphenamin from laboratory No. 4, sample C	31.49	5.89	5.34	0.2	13.20	2.38	1.7
Arsphenamin from laboratory No. 4, sample D	31.04	5.15	6.02	12.5	12.80	2.41	3.0
Arsphenamin from laboratory No. 5, sample E	30.87	5.14	6.00	12.5	13.05	2.36	0.8

Column 3 in Table 1 shows the percentages of arsenic in twelve lots of arsphenamin, each representing about 2,000 doses of 0.6 gm. each. Some of these values are close to the theoretical; most of them, however, are 1 per cent. lower; three preparations are 2 per cent. lower. As will be shown subsequently, it is best to consider the arsenic values in connection with nitrogen content and other data.

THE NITROGEN CONTENT OF ARSPHENAMIN

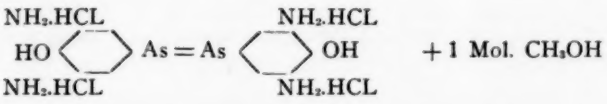
According to the formula, arsphenamin should contain 5.89 per cent. of nitrogen. A lower nitrogen content may be due to moisture, methyl alcohol or other organic solvents. Arsenical compounds con-

taining no nitrogen, as for instance arsenophenol, would lower the percentage of nitrogen. Dissymmetric compounds of the following type with lower amounts of nitrogen would have the same influence:



Inorganic arsenicals or other inorganic impurities would diminish the nitrogen.

The presence of tetramino-dihydroxy-arseno benzene tetrahydrochlorid,



which contains 9.8 per cent., can account for high nitrogen in arsphenamin. This compound can easily appear as an impurity since the commercial 3-nitro-4-hydroxyphenyl arsenic acid, from which arsphenamin is prepared, frequently contains the corresponding 3-5 dinitro compound.

Column 4 in Table 1 shows that the percentage of nitrogen in normal, as well as in toxic lots, of arsphenamin is near the theoretical amount. Most of the compounds show slightly lower values, probably indicating the absence of the tetramino compound.

Ratio of Arsenic to Nitrogen. — The quantitative estimation of either arsenic or nitrogen, or both in arsphenamin, does not give one a proper idea as to its purity. In order to evaluate properly its chemical purity, we should consider the ratio between the percentage of arsenic and that of nitrogen. The theoretical percentage of arsenic in arsphenamin is 31.6, of nitrogen 5.89 per cent.; the ratio is 5.37.

To illustrate the value of the arsenic nitrogen ratio, let us consider a sample of arsphenamin which on analysis showed an arsenic content of 32.55 per cent. (0.95 per cent. higher than the theoretical content) and a nitrogen content of 5.7 per cent. (0.2 per cent. lower than the theoretical content). The ratio between these two results is 5.7, or 0.33 greater than that of pure arsphenamin. This result, therefore, may be due to the presence of an impurity containing more arsenic and less nitrogen than arsphenamin, such as the corresponding polyarsenid. This contains 50.93 per cent. arsenic and only 2.38 per cent. of nitrogen, and is more toxic than arsphenamin. The arsenic and nitrogen contents of a mixture of 95 per cent. arsphenamin and 5 per cent. of the polyarsenid would correspond to the above high

ratio. Again, suppose a sample showed an arsenic content of 31.1 per cent. (0.5 per cent. lower than the theoretical content) and a nitrogen content of 6.28 per cent. (or 0.39 per cent. higher than the theoretical content). The corresponding ratio would be 4.95, or 0.42 less than that of pure arsphenamin. Such a condition may arise from the presence of an impurity containing less arsenic and more nitrogen than arsphenamin, as for example, tetramino-tetra hydroxy-arseno benzene tetra hydrochlorid, which contains 26.13 per cent. arsenic and 9.76 per cent. nitrogen. This is also more toxic than arsphenamin. The results obtained by the analysis of a mixture of 90 per cent. arsphenamin and 10 per cent. tetramino compound would give the above low ratio.

TABLE 3.—Toxicity of Various Compounds of Arsphenamin

Compound	Number of Patients	Dose Administered, Gm.	Clinical Reports, Symptoms *	Percentage of Animals That Survived Toxicity Tests†
2551	1 4 3	0.3 0.4 0.6	No reaction No reaction Slight reaction	100
2859	..	...	.....	Did not pass the toxicity test
3034	..	...	.....	Did not pass the toxicity test
3181	..	...	.....	Did not pass the toxicity test
3252	3 1 1	0.6 0.6 0.6	No reaction Fever, chills, headache, nausea, diarrhea Slight reaction	75
3350	1 1	0.6 0.6	No reaction Severe reaction, also vomited	75
3454	1 1 3 4 5 3 4 4 5 21	0.2 0.4 0.3 0.4 0.5 0.6 0.4 0.5 0.6 0.6	Immediate reaction Immediate reaction No reaction No reaction No reaction No reaction Vomiting Vomiting Fever, chills, headache, nausea, diarrhea Slight reaction	85

* The clinical reports in Tables 3 and 4 were obtained from Dr. Jay F. Schamberg, Department of Dermatology of the Polyclinic Hospital, Philadelphia.

† Rats in Tables 3 and 4 received 100 mg. of arsphenamin per kilo body weight. The number of animals which survived for seven days is expressed in per cent. Six or more rats were used in each test.

Finally, let us consider an example where the arsenic content is 30 per cent. (1.6 per cent. lower than the theoretical content) and the nitrogen content is 5.6 per cent. (0.2 per cent. lower than the theoretical content). The ratio between the two is 5.36, the theoretical value. This could be due to an impurity containing neither arsenic nor nitrogen, as for example, moisture, methyl alcohol or some inorganic substance which possesses no toxic properties.

Thus we see that a valuable measure of the chemical purity of arsphenamin lies in the ratio of arsenic to nitrogen.

Examination of columns 5 and 6 in Table 1 reveals a rather remarkable agreement with the theoretical arsenic nitrogen ratio. Such compounds as No. 3034, 3492, 3462, 3695 R_6 and 3181 have the theoretical ratio; those of other compounds are very nearly so. The highest deviation from the theoretical is only 3.4 per cent. Particularly interesting is the fact that Nos. 3492 and 3462, purposely selected for this work because they were found to produce immediate reactions and other untoward symptoms in patients, show the nearest values to the theoretical. They are better than those of lots which clinically and otherwise were found good. Moreover, lots Nos. 3034 and 3181, which were definitely rejected because they did not pass the animal toxicity standards, show theoretical arsenic nitrogen ratios.

TABLE 4.—Toxicity of Various Compounds of Arsphenamin

Compound	Number of Patients	Dose Administered, Gm.	Clinical Reports, Symptoms *	Percentage of Animals That Survived Toxicity Tests†
3462	1	0.6	Immediate reaction (convulsions)	100
	4	0.5	Vomiting	
	2	0.4	Vomiting	
	16	0.6	Slight reactions	
	21	0.6	No reactions	
3492	6	0.6	Vomiting	100
	6	0.6	Slight reactions	
	12	0.6	No reactions	
3695	1	0.6	No reactions	100
	1	0.6	Fever, chills, headache, nausea	
	1	0.6	Headache, nausea, vomiting	
8965-R_6	4	0.6	No reactions	100
	1	0.6	Headache, nausea, vomiting	
	1	0.6	Headache, diarrhea	
	1	0.6	Fever, headache, nausea	
3735	3	0.6	No reaction	75
	3	0.6	Slight reaction	

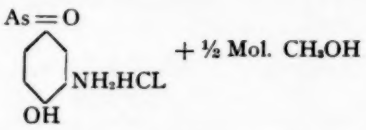
The values for the arsenic nitrogen ratio obtained with the arsphenamin produced at the Dermatological Research Laboratories indicate that the relationship between the arseno and amino groups is very close to that represented by its chemical formula. This fact tends to exclude the presence of such impurities as polyarsenids, tetramino, or any other compound in which the above relationship is different.

THE DEGREE OF REDUCTION OF ARSPHENAMIN ARSENIC TO OXYGEN RATIO

Arsphenamin belongs to that class of arseno compounds in which arsenic exists in the trivalent condition. Arseno compounds can be quantitatively oxidized by means of iodin solution or hydrogen peroxid,

forming the corresponding aryl-arsinic acids. Arsphenamin is thus converted into 3-amino-4-hydroxyphenylarsenic acid. Gaebel [5] suggested this reaction for the quantitative estimation of arsenic since the arseno group in arsphenamin is the only one which can be oxidized in the cold by iodin. In reality, by this method one determines the amount of oxygen absorbed by the arseno group. Ehrlich and Bertheim [2] and others obtained higher results by the gravimetric method. The incompleteness of oxidation has been explained by a reversible reaction. It is possible, however, that a small part of the arsenic in arsphenamin is present in oxidized form; hence the iodin value would be slightly diminished.

When 3-nitro-4-hydroxyphenylarsenic acid, from which arsphenamin is made, is not completely reduced, or if arsphenamin is permitted to oxidize, the latter is liable to contain a quantity of 3-amino-4-hydroxyphenylarsenous oxid, which has this formula:



When the above nitro-arsenic acid is reduced too far, the corresponding arsin compound might appear as an impurity. Both the arsenous oxid and arsin are more toxic than arsphenamin. The absorption of iodin can therefore serve as a quantitative method for the determination of the degree of reduction of arsphenamin. Low iodin value would indicate insufficient reduction or the presence of arsenous oxid, while high iodin value would indicate excessive reduction or the presence of arsin. In Table 1, the iodin values are presented in terms of milligrams of oxygen absorbed by 100 mg. of arsphenamin. The theoretical amount for 100 mg. of arsphenamin is 13.47 mg. of oxygen.

In order to determine whether a certain compound is over or under reduced, it is best to establish a relationship between the arsenic content and the oxygen value, because the latter value is dependent entirely on the arsenic radical, and hence on the amount of arsenic. For instance, No. 3695 required 13.35 mg. of oxygen, while No. 3454 absorbed only 12.75 mg. If the arsenic content is disregarded, it would appear that No. 3695 is further reduced than No. 3454. But No. 3695, as shown in column 3, contains more arsenic than No. 3454 and therefore must require more oxygen. Column 8 shows the ratios between milligrams of arsenic and milligrams of oxygen absorbed by 100 mg.

5. Gaebel, G. Otto: Titration von Salvarsan mit Jodlösung, Arch. d. Pharm. **249**:241, 1911.

of arsphenamin. The theoretical ratio is 2.34. Column 9 shows the percentage of deviation from the theoretical. It can be seen that these ratios differ but slightly from the theoretical ratio. The largest difference is only 4.3 per cent. It is evident that almost all of the compounds are pure as far as the degree of reduction is concerned.

Compounds which did not pass the animal toxicity test or were found to cause "reactions" in patients showed as good arsenic oxygen ratio as those which fulfilled all biologic requirements. It is evident, then, that the cause of toxicity or "reactions" cannot be attributed to the presence of arsenoxid or arsin.

METHODS OF ANALYSIS

Arsenic was determined gravimetrically by digesting with a mixture of nitric and sulphuric acid and finally precipitating with magnesia mixture according to the method outlined in U. S. Public Health Bulletin.[6]

The results obtained by this method were compared with those obtained by digesting with concentrated sulphuric acid alone, precipitating with hydrogen sulphid and finally precipitating with magnesia mixture.[7]

The results obtained by both methods were in close agreement. Only duplicate checking results were considered.

Nitrogen was determined by the ordinary Kjeldahl method and was frequently corroborated by the method of Dumas for nitrogen.

The oxygen absorption was estimated from the values obtained by titrating a water solution of arsphenamin with tenth normal iodin.

SUMMARY

1. The quantitative determination of arsenic alone in arsphenamin is insufficient to estimate its purity.

2. It is suggested to establish a ratio between the amounts of arsenic and nitrogen found by analysis.

3. The degree of reduction in arsphenamin is best judged by estimating the ratio between the arsenic content and the amount of oxygen absorbed.

4. The arsenic nitrogen and arsenic oxygen ratios indicate that various samples of arsphenamin are uniformly pure.

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6. U. S. Public Health Bull. **33**:1011, 1918.

7. Raiziss, G. W.; Kolmer, J. A., and Gavron, J. L.: Chemotherapeutic Studies on Organic Compounds Containing Mercury and Arsenic, J. Biol. Chem. **40**:533, 1919.

5. Judged by the arsenic nitrogen and arsenic oxygen ratios, various preparations of arsphenamin rejected because of greater toxicity or severe reactions in patients appear to be as pure as those satisfactorily passing all tests.

6. The analytical study of arsphenamin leads one to believe that the impurity causing reactions in patients is present only in very small quantities.

SUMMARY OF EXPERIMENTAL STUDIES ON THE HISTOPATHOLOGIC CHANGES PRODUCED BY ARSPHENAMIN AND NEO-ARSPHENAMIN *

JOHN A. KOLMER, M.D., AND BALDWIN LUCKE, M.D.
PHILADELPHIA

In determining the toxicity or organotropism of new compounds in the course of chemotherapeutic investigations, the general custom is to administer solutions to experimental animals and arrive at conclusions on the basis of dosage in relation to the duration of life. While the results are of much value, it would appear advisable to study the less toxic and promising compounds for the kind and degree of tissue injury which they may produce in experimental animals as an additional criterion of suitableness for the treatment of disease among persons and as a guide in the preparation of new chemical compounds not only of least toxicity, but which are also least likely to produce tissue injury.

The purpose of our investigations was to study the histopathologic changes produced in rats and rabbits by the intravenous injection of single large and multiple small doses of arsphenamin and neo-arsphenamin [1] as bearing on the use of these compounds for the treatment of disease among persons and in relation to chemotherapeutic studies with new arsenical compounds prepared by one of us (Kolmer) in association with Dr. Schamberg and Dr. Raiziss.

The fatalities following the administration of arsphenamin and neo-arsphenamin in the treatment of syphilis have usually been attributed to the toxicity of the drugs and to technical errors in administration referable to the preparation of the solutions and manner of injection.

The results of studies of the gross and histologic tissue changes have usually shown the presence of some form of acute nephritis and

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* Read before the joint meeting of the Section on Pharmacology and Therapeutics and the Section on Dermatology at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

* From the Dermatological Research Laboratories of Philadelphia and the McManes Laboratory of Pathology of the University of Pennsylvania.

* Investigation aided by funds accruing from the preparation of arsphenamin and neo-arsphenamin.

1. Kolmer, J. A., and Lucke, B.: An Experimental Study of the Histopathological Changes Produced by Arsphenamin, Arch. Derm. & Syph. (in press); ibid.: An Experimental Study of the Histopathological Changes Produced by Neo-Arsphenamin, Arch. Derm. & Syph. (in press).

degenerative changes in the liver as the most prominent lesions. In Europe an acute hemorrhage meningitis has been commonly described whereas in America few or no changes in brain, cord and meninges have been found. Under these circumstances, however, but limited information can be gained regarding the tissue changes strictly ascribable to the solutions of the drugs themselves because of pathologic changes in the organs and tissues due to syphilis, for which the majority of the patients were being treated.

In our experiments rats and rabbits were injected intravenously with acid solutions of arsphenamin, that is, non-neutralized solutions in water which are extremely toxic; also with single large (0.080 to 0.100 gm. per kilo of body weight) and multiple small (0.01 mg. per kilo) doses of solutions of disodium arsphenamin prepared by adding about one-third excess of the amount of solution of sodium hydroxid required to precipitate and "clear" the solution. The single large doses corresponded to 4.8 and 6 gm. for a person of about 130 pounds. The small dose corresponded to 0.6 gm. per 130 pounds, being the maximum amount administered to persons at one time; from six to seventeen doses were administered.

Neo-arspenamin was injected into rats and rabbits in single large (0.200 gm. per kilo) and in multiple small doses (0.02 to 0.03 gm. per kilo). The former corresponded to about 12 gm. per 130 pounds and the latter to 1.2 to 1.8 per 130 pounds, from six to eighteen doses of the latter being administered.

Necropsy examinations of animals were made at varying intervals after injection, and the following organs subjected to histologic study: Cerebrum, cerebellum, brain stem and meninges, heart, lungs, liver, kidneys, suprarenals and spleen.

The histopathologic changes have varied in degree among animals receiving the same compound under identical conditions and have generally been somewhat more severe among the rats than among the rabbits.

RESULTS OF EXPERIMENTS

The tissue injuries produced by neo-arsphenamin have generally been of the same character as those produced by arsphenamin, but, in comparison to dosage, have been less severe.

Acid or non-neutralized solutions of arsphenamin produced severe vascular injuries in all organs, characterized by congestion, hemorrhagic extravasations and the production of peculiar thrombi composed presumably of precipitates, conglutinated and hemolyzed erythrocytes. Secondary cellular degenerations and necroses followed.

Single large doses of arsphenamin and neo-arsphenamin also produced similar vascular changes of congestion, hemorrhage and thrombi

of conglutinated erythrocytes in the various organs, but in a much milder degree; areas of focal necrosis and cellular degenerations in heart muscle, liver and spleen were rather prominent. The kidney lesions were composed of these vascular changes and varying degrees of tubular necrosis; the suprarenals showed well marked changes in lipoid and chromaffin contents in addition to vascular changes and cellular degenerations.

Multiple small doses of arsphenamin and neo-arsphenamin produced slight vascular changes of congestion and thrombi of conglutinated erythrocytes in the various organs; focal areas of cellular degenerations and necroses were frequently well marked, particularly in the heart and liver. The kidneys usually showed vascular and tubular changes, and the suprarenals various changes, including alterations in the lipoid and chromaffin contents.

Details regarding all of these changes observed after the administration of the different solutions of arsphenamin and neo-arsphenamin are given in the papers previously mentioned.[1]

It is to be emphasized that the maximum changes were produced by large doses of acid or non-neutralized solutions of arsphenamin, and by doses of disodium arsphenamin and neo-arsphenamin so large that they have no analogy to the amounts commonly administered to persons in one dose and at one time. While well marked tissue changes were produced by amounts of disodium arsphenamin and neo-arsphenamin comparable to the doses administered to persons in the treatment of syphilis and other infections, we do not wish to create any unfavorable impression against arsphenamin and neo-arsphenamin which have proved so valuable as therapeutic agents. *The arsphenamins and neo-arsphenamins prepared by these different laboratories produced similar changes.*

We simply wish to record the fact that neo-arsphenamin is less apt to produce these tissue injuries than arsphenamin, and to advance our knowledge of specific arsenic therapy as a means toward facilitating the more successful treatment of syphilis and other infections with arsenical compounds with the least possibility of producing tissue injury.

SOME SALIENT FACTS REGARDING THE TOXICITY OF ARSPHENAMIN AND NEO-ARSPHENAMIN *

GEORGE B. ROTH, M.D.
Pharmacologist, Hygienic Laboratory, U. S. Public Health Service
WASHINGTON, D. C.

INTRODUCTION

The introduction of the newer arsenicals, arsphenamin and neo-arsphenamin,[1] in the treatment of syphilis brought into prominence the intravenous method of administration, formerly a less extensively used method. The intravenous method is generally considered the most effective method to use in administering these compounds, but by many it is considered more hazardous to the patient than either the subcutaneous or intramuscular methods. For these reasons, especially, the compounds should be made as free from objectionable impurities as possible; furthermore, the limitations and dangers of the intravenous method of administration should be of prime importance to syphilographers. Studies now in progress at the Hygienic Laboratory, dealing directly with the routine conduct or modifications of the official biologic tests for arsphenamin and neo-arsphenamin intended for shipment from one state to another, indicate some of the factors that may be responsible for untoward results when these drugs are administered intravenously.

OFFICIAL METHOD FOR TESTING ARSPHENAMIN AND NEO-ARSPHENAMIN

In the official method for testing arsphenamin, it is required that white rats weighing from 100 to 150 gm. shall tolerate 100 mg. per kilogram of the drug for forty-eight hours when given intravenously as a 2 per cent. alkaline solution, 0.9 c.c. of normal sodium hydroxid being used for 100 mg. of arsphenamin. White rats are required to tolerate 200 mg. per kilogram of neo-arsphenamin for seven days when given intravenously as a 4 per cent. aqueous solution. It is further required that for both compounds the rate of injection shall be 12 to 15 seconds for every 0.1 c.c. of solution.

CHEMICAL NATURE OF ARSPHENAMIN AND NEO-ARSPHENAMIN

Arsphenamin is the dihydrochlorid of 3,3′-diamino-4,4′-dihydroxy-arsenobenzene, while neo-arsphenamin is sodium 3,3′-diamino-4,4′-

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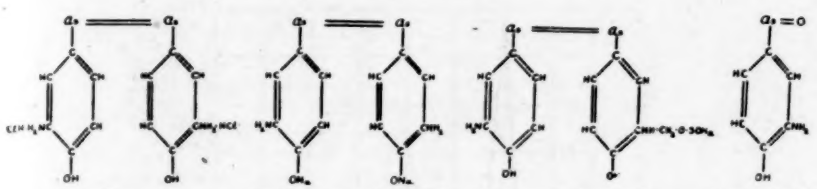
* Read before the joint meeting of the Section on Pharmacology and Therapeutics and the Section on Dermatology at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

1. These refer to the chemical equivalent of 606 and 914, formerly known exclusively as salvarsan and neosalvarsan.

dihydroxyarsenobenzene-N-methylene sulphinate. When arsphenamin is properly made alkaline with sodium hydroxid, as is required before its administration, the disodium salt of 3,3′-diamino-4,4′-dihydroxy-arsenobenzene is formed. If oxidation occurs in any of these compounds, the more toxic substance 3-amino-4-hydroxyphenylarsenoxid may be formed. This more toxic compound is frequently referred to as "arsenoxid," and is a cleavage product in which only one arsenic atom exists in the molecule. The structures of these compounds are illustrated by the following formulae:



Arsphenamin. Sodium arsphenamin. Neo-arsphenamin. Arsenoxid.

BEHAVIOR OF ARSPHENAMIN AND NEO-ARSPHENAMIN IN THE BODY

Neo-arsphenamin is regarded by many simply as arsphenamin in a convenient form for administration. From the formula alone it is seen that neo-arsphenamin is a modified arsphenamin and, as will be shown later, neo-arsphenamin is distinctly unlike arsphenamin as regards its behavior in the animal organism.

A statistical study of the death rate and time of death of the rats used in the official testing of arsphenamin examined during September and October, 1919, showed that a little over 80 per cent. of the animals that died within fourteen days did so within twenty-four hours, and that almost 90 per cent. of the deaths occurred within the first forty-eight hours (Chart 1). On the other hand, similar computations for neo-arsphenamin gave figures which contrasted markedly with those obtained for arsphenamin. Approximately 5 per cent. of the deaths from neo-arsphenamin occurred within the first day, 15 per cent. within the first two days, 30 per cent. within the first three days and 60 per cent. within the first four days. The highest death rate from neo-arsphenamin occurred on the fourth day. Within the fifth day the death rate was about 75 per cent. After the fifth day the death rate closely approached the curve for the death rate in "normal" animals (Chart 2).

The death rate for the entire fourteen day period is given in Table 1.

TABLE 1.—Death Rate and Time of Death in Rats After the Administration of Arsphenamin and Neo-arsphenamin

	Number of Days after Injection							
	1	2	3	4	5	6	7	8th to 14th inclusive
Rats treated with arsphenamin: Number of deaths	139	9	4	3	0	2	0	12
Rats treated with neo-arsphenamin: Number of deaths	5	10	19	37	11	6	5	19

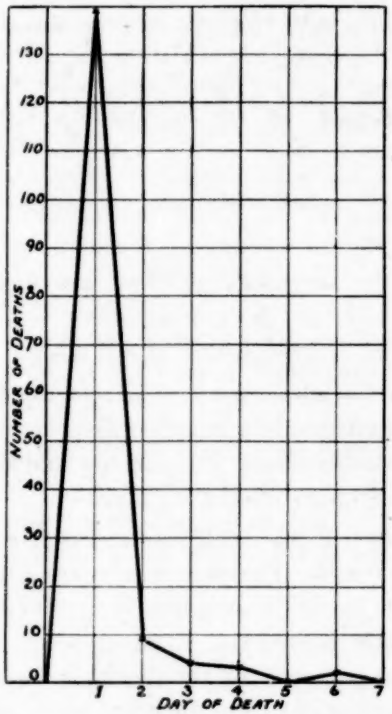


Chart 1.—Death rate and time of death of rats treated with arsphenamin.

The total number of rats injected with arsphenamin was 475, with neo-arsphenamin, 515.

Comparison of the death rate in treated and nontreated rats shows that of the 1,470 rats purchased by the laboratory from Oct. 14, 1919, to Jan. 14, 1920, only seventy-four, or about 5 per cent., of the nontreated animals died before being injected. The death rate after the second day in rats treated with arsphenamin when based on the total number of rats injected, was about 4 per cent; similarly after the

seventh day in rats treated with neo-arsphenamin the death rate was about 4 per cent.

From the data given above it is evident that the two compounds behave differently in the rat, arsphenamin producing death only a short period after its administration, whereas neo-arsphenamin kills relatively slowly. An acute death after neo-arsphenamin in rats is relatively rare when tested at the official dosage, whereas after arsphenamin it is the rule. Furthermore, neo-arsphenamin rarely causes immediate symptoms in the rat, while arsphenamin usually causes rather pronounced depression when these compounds are given intravenously in the standard test doses.[2]

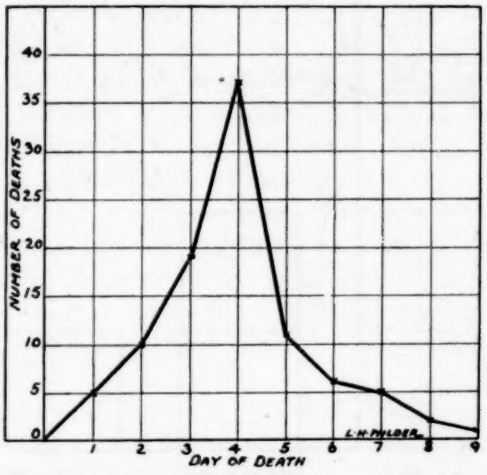


Chart 2.—Death rate and time of death of rats treated with neo-arsphenamin.

EFFECT OF CONCENTRATION OF THE SOLUTION ON THE TOXICITY OF ARSPHENAMIN

It was previously noted that the concentration of the solution of arsphenamin seemed to modify the toxicity to some extent.[3]

Quite recently Dr. G. W. McCoy, director of the Hygienic Laboratory of the United States Public Health Service[4] called attention to the fact that on investigation of the untoward results that have been reported to the Hygienic Laboratory from the use of arsphenamin made by the various American producers, it was almost invariably

2. Rats injected intravenously with neo-arsphenamin bleed profusely while those injected with arsphenamin bleed but little. The effects of the two compounds on the coagulation of blood in vivo, therefore, are strikingly unlike.

3. Roth, George B.: Hygienic Lab. Bull., No. 113, July, 1918.

4. McCoy, G. W.: The Administration of Arsphenamin. J. A. M. A. **72**:1386, 1919.

found that the drug had been administered in either too concentrated solution or at a too rapid rate. He therefore directed attention to these points and warned against the use of too concentrated solutions and urged that due attention should be paid to rate of administration.

On the other hand, Nelken [5] considers that concentrated solutions given rapidly are as safe as the more dilute solutions given slowly.

Pusey [6] states that while it is true that animal experiments have shown arsphenamin to be less toxic when well diluted, the necessity for highly dilute solutions arises only when arsphenamin is contaminated by toxic substances.

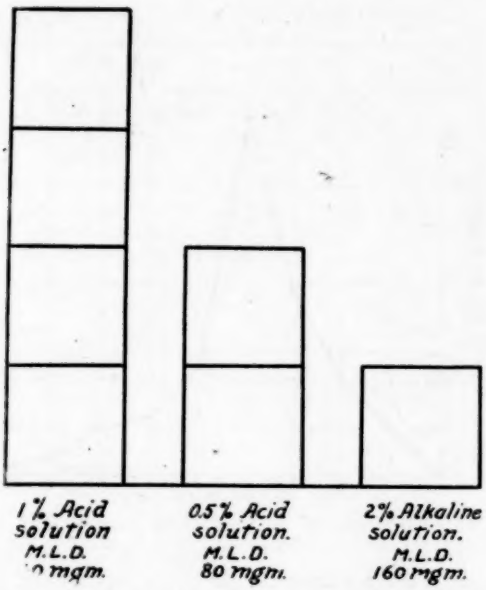


Chart 3.—Toxicity of arsphenamin before and after alkalinization.

Experiments have lately been carried out on white rats in which the official rate of administration was used, which demonstrate that the toxicity of arsphenamin under certain conditions increases as the concentration increases. The increase in toxicity is strikingly demonstrated by the more toxic acid solutions of arsphenamin. When acid solutions of arsphenamin were given intravenously to white rats, it was found that the minimal lethal dose of a high grade preparation [7] was 80 mg. per kilo when given as a 0.5 per cent. solution, and 40 mg. per kilo when administered as a 1 per cent. solution.

5. Nelken, A.: Administration of Arsphenamin, J. A. M. A. **72**:1695, 1919.

6. Pusey, William Allen: Administration of Arsphenamin, J. A. M. A. **72**: 1786, 1919.

7. This arsphenamin passed the official test at 140 mg. per kilo, the minimal lethal dose being 160 mg. per kilo

These findings not only indicate that concentration is a factor in modifying the toxicity of acid solutions, but in addition show that dilute acid solutions of arsphenamin may be given intravenously if properly administered, the above preparation in dilute acid solution having complied with the standard required for alkaline solutions of arsphenamin made by the American producers during the early period of their existence. However, it should not be inferred from this that acid solutions should be used clinically.

In this connection it is interesting to compare the toxicity of the same arsphenamin as an acid solution and as an alkaline solution. As a 2 per cent. alkaline solution the minimal lethal dose was found to be 160 mgm. per kilo, hence it is seen that as a 1 per cent. acid solution the toxicity is four times, and as a 0.5 per cent. acid solution, twice as great as a 2 per cent. alkaline solution (Chart 3).

Using a different brand of arsphenamin than the one used for determining the toxicity of acid solutions, comparative experiments were made to determine the relative toxicity of 2 and 0.5 per cent. solutions which were made alkaline with 1.06 c.c. normal sodium hydroxid per 100 mg. of arsphenamin. These solutions were administered to white rats intravenously at the same rate. The animals in each group, except in groups A and AB, received the drug alternately as a 2 and 0.5 per cent. solution. The animals in each group were from the same stock and varied but little in their weight and condition.

Except in groups A and AB, the 0.5 per cent. solution was made from the 2 per cent. solution by diluting with distilled water. The experiments appear in detail in Table 2.

TABLE 2.—Toxicity of Arsphenamin in White Rats When Given Intravenously Either as a 2 or 0.5 Per Cent. Alkaline Aqueous Solution

Group	2 per Cent. Solution					Group	0.5 per Cent. Solution				
	Dose Mg.	No. Injected	No. Died in 48 Hrs.	No. Died in 14 Days	No. Lived 14 Days		Dose, Mg.	No. Injected	No. Died in 48 Hrs.	No. Died in 14 Days	No. Lived 14 Days
A	140	5	5	5	0	AB	140	5	2	2	3
B	140	5	5	5	0	B-1	140	5	3	3	2
C	140	5	3	3	2	C-1	140	5	4	4	1
D	140	5	4	5	0	D-1	140	5	3	4	1
Totals 140 mg. dose	...	20	17	18	2	....	...	20	12	13	7
Per cent.	...	..	85	90	10	....	...	..	60	65	35
E	120	5	4	4	1	E-1	120	5	5	5	0
F	120	5	1	1	4	F-1	120	5	2	2	3
G	120	5	2	3	2	G-1	120	5	0	0	5
H	120	5	0	2	3	H-1	120	5	0	0	5
Totals 120 mg. dose	...	20	7	10	10	....	...	20	7	7	13
Per cent.	...	..	35	50	50	....	...	..	35	35	65

These experiments with alkaline arsphenamin indicate that the toxicity is increased but slightly as the concentration is increased from 0.5 to 2 per cent., provided the solutions are given slowly.

INFLUENCE OF THE RATE OF INJECTION OF ARSPHENAMIN ON TOXICITY

The influence of the rate of injection of arsphenamin solutions on their toxicity was determined in guinea-pigs. The variation inherent in the animals themselves, when obtained from different sources, was eliminated by using animals obtained from the same source of supply in each series of experiments.

These experiments were carried out in two ways. In groups M and N, using guinea-pigs of practically the same weight and condition, the ten animals of each group were given 40 mg. of arsphenamin per kilo as a 2 per cent. alkaline solution intravenously; the first five received the drug rapidly, that is, in from 6 to 10 seconds, while the second five received the same solution slowly, that is, in from 95 to 128 seconds.

In groups O, P, Q and R, the 10 guinea-pigs of each group received the drug alternately rapidly and slowly; that is, animal number one received the drug rapidly, while animal number two received it slowly, and so on through the set, the dosage being 50 mg. per kilo. The summarized results are given in Table 3.

TABLE 3.—THE INFLUENCE OF RATE OF INJECTION OF ARSPHENAMIN IN GUINEA-PIGS WHEN GIVEN INTRAVENOUSLY AS A 2 PER CENT. ALKALINE AQUEOUS SOLUTION PER LEG VEIN

Group	Rapid Injection				Slow Injection			
	Number Injected	Number Died in 48 Hours	Number Died in 14 Days	Number Lived 14 Days	Number Injected	Number Died in 48 Hours	Number Died in 14 Days	Number Lived 14 Days
M	5	2	2	3	5	0	0	5
N	5	0	0	5	5	0	0	5
O	5	5	5	0	5	0	3	2
P	5	1	4	1	5	1	4	1
Q	5	5	5	0	5	0	0	5
R	5	4	4	1	5	1	3	2
Totals	30	17	20	10	30	2	10	20
Per cent.	..	57	67	33	..	7	33	67

Table 3 shows clearly that the slow injection of arsphenamin into guinea-pigs is much better tolerated than rapid injection, the mortality within forty-eight hours after rapid injection being many times greater than after slow injection. From these experiments we conclude that the rate of administration is a potent factor in modifying the toxicity of arsphenamin, the toxicity increasing as the rate is

increased. Furthermore, the depression which occurs subsequent to the injection is more pronounced after rapid than after slow injection.

RELATION OF SOLUBILITY OF NEO-ARSPHENAMIN TO TOXICITY

The degree and ease of solubility of neo-arsphenamin have been found to be intimately associated with its toxicity. Preparations which were found to be incompletely soluble within 10 to 15 minutes when made up as 4 per cent. aqueous solutions, were found to kill one or more rats in every official test. In twenty-two tests which represented seventeen lots of incompletely soluble neo-arsphenamins in which 110 rats, or twenty-two sets of five each, were used, only thirty-one rats survived. In eighteen of these sets three or more animals died, in two sets two in each set died, while in the remaining two sets but one rat in each set died. The amount of insoluble matter contained in these samples was usually slight and consisted of a small amount of flocculent material which would settle in a few minutes, leaving only a film on the bottom of the mixing cylinder, while in other cases the amount was considerable. In most of these cases only the supernatant clear liquid was injected; in other cases the solutions were filtered through a soft paper filter. Filtration, however, did not cause any marked decrease in toxicity. Tests were made with two samples to determine the effect of filtration. In one sample the filtered solution killed eight of ten rats at the official dose, while the unfiltered solution killed all of ten rats injected in the same manner. In the second sample the result was practically the same as the preceding.

All of these preparations were reported by the manufacturer to be readily soluble in his tests so that the decrease in solubility mentioned above probably occurred after the products left the factory. As it cannot be definitely stated whether these preparations would have passed the official toxicity tests conducted by the Hygienic Laboratory before the preparations became less soluble, positive conclusions are unwarranted from the above findings. In the manufacturers' tests, however, all of these preparations were of satisfactory toxicity.

From these observations we have come to regard incompletely or slowly soluble products as dangerous, even if filtered. The marked toxicity noted above may have been due either to an increase in the amount of shaking of the solution or to the physical state of the product itself. The latter explanation seems the more probable as the amount of shaking in the above experiments was no more than was done when completely soluble preparations of satisfactory toxicity were examined.

THE EFFECT ON TOXICITY OF SHAKING A SOLUTION OF NEO-ARSPHENAMIN OR ARSPHENAMIN IN THE PRESENCE OF AIR

Neo-arsphenamin.—When neo-arsphenamin is dissolved in freshly glass distilled water as a 4 per cent. solution and shaken vigorously[8] by hand with about twice its volume of air, it rapidly increases in toxicity, presumably from the formation of "arsenoxid." In most of the tests a domestic neo-arsphenamin (P — 4) was used to determine the effect of shaking. This preparation was an unusually high grade preparation passing the official tests at 420 and failing at 500 mg. per kilogram of rat. When this preparation was made up as a 4 per cent. aqueous solution and shaken vigorously by hand in a glass-stoppered 25 c.c. cylinder at room temperature (about 20 degrees C.), its toxicity was over four times as great as that of the unshaken solution. When shaken for 5 minutes, it failed to pass at the official dosage of 200 mgm. and when shaken for 1 minute it failed to pass at a dosage of 300 mg. and gave only a 60 per cent. pass at both 200 mg. and 140 mg. dosages.

Vigorous shaking for one minute in the presence of air will therefore increase the toxicity of high grade neo-arsphenamin considerably and thereby render it a dangerous borderline product. There was no color change in this product (P — 4) even after shaking for 10 minutes in the manner described above.

By using a lower grade domestic neo-arsphenamin (B — 4), it was found that vigorous shaking for one minute in the presence of air resulted in a complete failure when tested at the standard test dose of 200 mg. When tested in the official manner as an unshaken solution, this preparation passed at 200 mg., but failed at 240 mg. per kilogram. It was unlike P — 4 in that a slight deepening of the light canary yellow solution to a deep golden yellow occurred after shaking for ten minutes. However, after shaking for one minute no color change was detected in this preparation (B — 4).

Arsphenamin.—The effect on toxicity of shaking a solution of arsphenamin was determined by using an alkaline solution of arsphenamin, the amount of alkali added being a trifle greater than was required to form the disodium salt, that is, 1 c.c. of normal sodium hydroxid was added for every 100 mg. of arsphenamin.

For these experiments a domestic arsphenamin (B — 2) was used. This lot passed the official tests at 140 and failed at 160 mg. per kilo (see Table 4).

After making a 2 per cent. aqueous alkaline solution of disodium arsphenamin as described above, it was shaken vigorously in a 25 c.c.

8. Approximately 230 excursions per minute.

glass-stoppered cylinder at room temperature in the presence of about twice its volume of air for a period of ten minutes. When tested on rats in the official manner, eight of ten rats died at a dosage of 100 mg. per kilo, while only two of ten rats died when given a similar dose of the unshaken solution.

The symptoms after the administration of the shaken solution were especially severe, the animals developing marked dyspnea and extreme weakness immediately after the injection. These symptoms lasted for about an hour. The control animals which received the unshaken solution became slightly drowsy, but were able to walk immediately after the injection.

These experiments conclusively show that the toxicity of a solution of arsphenamin as prepared for administration to man is materially increased by shaking for ten minutes in the presence of air, and that vigorous shaking should be avoided after the alkali is added. Unlike neo-arsphenamin, the solution was distinctly darkened after shaking for several minutes, and decidedly darkened after shaking for ten minutes.

COMPARISON OF THE TOXICITY OF ARSPHENAMINS AND NEO-ARSPHENAMINS MADE IN THE UNITED STATES WITH THOSE OF FOREIGN MANUFACTURE

It is generally recognized that the standards set by the Hygienic Laboratory for the purity of arsphenamin and neo-arsphenamin are sufficiently rigid to insure products of high quality. In order to ascertain whether United States products compared favorably with foreign products a toxicologic study was made of five arsphenamin and five neo-arsphenamin preparations made in the United States, also

TABLE 4.—COMPARATIVE TOXICITY OF ARSPHENAMIN AND NEO-ARSPHENAMIN PREPARATIONS MADE IN THE UNITED STATES WITH THOSE OF FOREIGN MANUFACTURE

Sample of Arsphenamin	Maximal Tolerated Dose, Mg. per Kilo.	Minimal Lethal Dose, Mg. per Kilo.	Arsenic Content, per Cent.	Sample of Neo-Arsphenamin	Maximal Tolerated Dose, Mg. per Kilo.	Minimal Lethal Dose, Mg. per Kilo.	Arsenic Content, per Cent.
U. S. Products:				U. S. Products:			
B-1	100	120	31.3	B-3	200	240	19.0
B-2	140	160	29.8	B-4	200	240	18.4
P-1	180	220	31.3	P-3	280	320	18.8
P-2	120	140	30.5	P-4	420*	500	19.5
C-1	160	180	31.5	C-2	240	280	18.6
Foreign Products:				Foreign Products:			
German H-1	80	100	32.1	German H-4	260	300	19.7
German H-2	120	140	32.0	German H-5	240	300	18.8
German H-3	60	80	31.0	French B-1	240	280	19.5
French S-1	60	80	30.0	French S-2	120	150	19.8
Canadian M-1	80	100	24.9	Canadian T-1	200	240	18.8
Japanese T-1	140	160	31.8	Japanese T-2	360+	?	17.7

of six arsphenamin and six neo-arsphenamin preparations of foreign manufacture. These preparations were all administered intravenously to white rats in the official manner, the minimal lethal dose for arsphenamin being the minimal dose which killed 60 per cent. or more of the animals within forty-eight hours, whereas for neo-arsphenamin the minimal lethal dose refers to the minimal dose which killed 60 per cent. or more of the animals within seven days. The results of this study are summarized in Table 4.

It may be concluded from this study that the arsphenamins made in the United States are generally less toxic than those of foreign manufacture, while the domestic neo-arsphenamins compare favorably with the foreign neo-arsphenamins examined and in certain instances are decidedly less toxic than most of the foreign products.

CONCLUSIONS

The results of the foregoing experiments warrant the following conclusions:

1. Neo-arsphenamin behaves differently in the animal organism from arsphenamin and should not be regarded simply as arsphenamin in a convenient form for administration.

2. When administered intravenously and at a constant rate, acid solutions of arsphenamin are much more toxic than the corresponding alkaline solutions, the toxicity of the acid solutions increasing with the concentration.

3. A properly alkalinized 2 per cent. arsphenamin solution when administered intravenously and in high dosage is slightly more toxic than a 0.5 per cent. solution.

4. The toxicity of properly alkalinized arsphenamin increases greatly as the rate of its intravenous administration is increased. Rate of administration is, therefore, an important factor in determining toxicity.

5. When neo-arsphenamin is found to dissolve with comparative difficulty, it is generally highly toxic and should be discarded.

6. Shaking aqueous solutions of neo-arsphenamin or alkalinized arsphenamin in the presence of air increases their toxicity markedly. When a 4 per cent. solution of neo-arsphenamin is shaken vigorously for ten minutes its toxicity is more than quadrupled.

7. Arsphenamin preparations made in the United States are generally less toxic than those of foreign manufacture.

8. Neo-arsphenamin preparations made in the United States compare favorably, and in certain instances are decidedly less toxic than most of the foreign products.

THE APPLICATIONS AND LIMITATIONS OF THE ARSPHENAMINS IN THERAPEUTICS*

JOHN H. STOKES, A.B., M.D.

Chief of the Section on Dermatology and Syphilology, Mayo Clinic; Associate Professor of Medicine, the Mayo Foundation, University of Minnesota

ROCHESTER, MINN.

Ten years have now elapsed since Ehrlich announced the synthesis of arsphenamin and expressed his hopes for its therapeutic efficacy in syphilis in man based on its effect on the disease in the rabbit. The failure of the simple, experimentally determined rationale of the single dose cure, when applied to man, abruptly precipitated the use of the drug on a period of quasi-empiricism from which we are now slowly emerging. In fact, many valuable empiric rules of thumb which have marked our progress along the way of rationalization still survive. The one great solvent of therapeutic perplexities, time, has not yet had its full say on the ultimate values of the arsphenamin in syphilis. In frambesia, relapsing fever, rat-bite fever, and other less resistant spirilloses, the question is perhaps settled. But until a generation of syphilitic humanity, treated with arsphenamin, has been born, studied, died and passed through a gross and microscopic necropsy examination whose searching quality we are only beginning to appreciate, the full applications and limitations of the arsphenamins in the therapeusis of the disease are open to discussion.

Within the last few years the experimental and analytic basis for a new rationale of arsphenamin therapy has developed rapidly. Among notable contributions one recalls the basic work of Warthin [1] on the pathology of the disease; Noguchi and Akatsu,[2] Nichols [3] and

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*This discussion is based on material collected from a series of 30,000 intravenous injections of arsphenamin under hospital conditions. Where the term "injection" is used without modification in connection with arsphenamin, intravenous injection should be understood.

*Read before the joint meeting of the Section on Pharmacology and Therapeutics and the Section on Dermatology at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

1. Warthin, A. S.: The New Pathology of Syphilis, Am. J. Syph. **2**:425, 1918; The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or "Cured" Syphilis, Am. J. M. Sc. **152**:508, 1916.

2. Noguchi, H., and Akatsu, S.: Immunological Studies on pure Cultures of Various Spirochetes, J. Exper. Med. **25**:765, 1917.

3. Nichols, H. J.: Observations on the Pathology of Syphilis, J. A. M. A. **62**:466 (Aug. 8) 1914.

Reasoner [4] on spirochetal strains, the investigations of Akatsu and Noguchi [5] on the arsenical and mercurial tolerance of spirochetes; the studies of Danysz,[6] Rieger,[7] Schamberg [8] and his collaborators on the biochemistry and toxicology of the arsphenamins, and the work of Friedberger and Masuda, Weisburg, Bachucke, Toyama and Kolmer [9] on the nonspecific formation of agglutinins, hemolysins and other antibody-like substances, under the influence of the drug. From one or another phase of this work have sprung various efforts of syphilographers of experience [10] to apply to therapeutics the principles suggested by laboratory research, as in the intensive technic proposed by Pollitzer,[11] and the utilization of antibody effects in the intraspinous technic of Swift and Ellis.[12] These rationalizations are not made any less commendable in intent by the fact that cures, as determined by reinfection, may be the sequels of the most irrational and haphazard procedures. Contemplation of the reinfection field in the literature is the best antidote for the conception that there is a standard arsphenamin treatment for the cure of a resistant spirillosis such as syphilis. Almost anything will cure some patients, almost nothing avails in others. A discussion of arsphenamin therapy must therefore take cognizance to a high degree of the fact that the drug is only one factor in a complex, and that what it accomplishes in one case may be no guide to its efficacy in another. It is merely one of the factors in the

4. Reasoner, M. A.: Some Phases of Experimental Syphilis with Special Reference to the Question of Strains, J. A. M. A. **67**:1799 (Dec. 16) 1916; Early Death from Cerebral Syphilis, with Successful Rabbit Inoculation, J. A. M. A. **66**:1917 (June 17) 1916.

5. Akatsu, S., and Noguchi, H.: The Drug-Fastness of Spirochetes to Arsenic, Mercurial and Iodid Compounds in Vitro, J. Exper. Med. **25**:349, 1917.

6. Danysz, J.: Les propriétés physicochémiques des produits du groupe des arsénobenzenes, leurs transformations dans l'organisme, Ann. d. l'Inst. Pasteur **31**:114, 1917.

7. Rieger, J. B.: Notes on the Decomposition of Arsphenamin, J. Lab. & Clin. Med. **4**:181, 1918.

8. Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Experimental and Clinical Studies of the Toxicity of Dioxydiamino-Arsenobenzol Dichlorhydrate, J. Cutan Dis. **35**:286, 1917.

9. Toyama, I., and Kolmer, J. A.: The Influence of Arsphenamin and Mercuric Chlorid on Complement and Antibody Production, J. Immunol. **3**:301, 1918. (This article is particularly valuable.)

10. Schreiber, E.: Ueber die Wirkungsweise des Salvarsans und Quecksilbers bei der Syphilis, München. med. Wchnschr. **61**:522, 1914.

11. Pollitzer, S.: The Principles of the Treatment of Syphilis, J. Cutan. Dis. **34**:633, 1916.

12. Swift, H. F., and Ellis, A. W.: The Treatment of Syphilitic Affections of the Central Nervous System with Special Reference to the Use of Intraspinous Injections, Arch. Int. Med. **12**:331, 1913. Swift, F.: A Study of Serum Salvarsanized in Vitro, J. Exper. Med. **24**:373, 1916.

course of the disease. The specificity and mathematical exactness of its effects in given dosages, of which Ehrlich dreamed, has gone glimmering among the pitfalls of spirochetal individuality and variations in human susceptibility. No amount of the drug by any technic of administration can avail, it would seem, in the face of a combination of a given low specific tissue resistance in the patient, and a high selective tendency to localize in the same tissue on the part of the infecting organism. A susceptible nervous system and a neurotropic spirochete probably explain some of the most conspicuous failures of arsphenamin. To work out the possibilities of the arsphenamin factor in the outcome of any disease in its relation to the potentialities of the infecing organism and the resistance of the patient is the ultimate problem of arsphenamin therapeusis.

TWO METHODS OF ADMINISTRATION OF ARSPHENAMIN

Broadly speaking, two types of therapeutic employment of the arsphenamins are recognizable. While the two overlap to some extent and each contains some elements of the other, an appreciation of their respective merits and defects contributes much to the rationalizing of arsphenamin procedure. Massive or intensive technic aims primarily at spirocheticidal effects and sacrifices the immunizing or resistance-building powers of the drug. Such a technic calls for the highest possible concentration of the drug in the blood and tissues, maintained for the longest possible time which the patient's tolerance will permit. The methods employed for this purpose vary from the administration of small daily doses of a decigram or two for a number of days, to the administration of maximum doses for two or three days in succession, followed by a rest period or a change to some other mode of treatment. Such methods, I believe, involve an increased risk of cumulative toxic effects and of failure as expressed in the occurrence of neurosyphilitic accidents, which must be compensated for by a demonstrated superiority in the form of a high percentage of cures. I do not think there exists conclusive evidence demonstrating such a superiority. For this reason, I feel that the safer plan for the average case is a combination of massive and immunizing technic.

The logical field for massive technic is the stage of the disease in which the infecting organism is accessible both in blood stream and tissues, where it can feel the full force of the direct spirillicidal action. In the later stages, when the organism is walled off by the infiltrations and fibroses so distinctive of the pathology of syphilis, and protected from the action of blood-borne therapeutic agents by endarteritic occlusion of the blood supply, it seems to me that the hope of radical spirillicidal action is illusory and not to be depended on. In its place we must substitute a stimulation of the native or intrinsic protective

mechanism of every tissue of the body. In syphilis at least, I question whether this mechanism has the high degree of specificity so often credited to it. It is perhaps proteolytic and bacteriolytic rather than purely spirocheticidal. If we are to employ a drug such as arsphenamin at such a stage, we should, it seems to me, employ it by a technic which brings out more of its immunity-stimulating power, even though it may be at a sacrifice of some of its direct spirillicidal action. That the sacrifice of its direct spirillicidal action is not as complete in less massive technics than some observers seem to believe, is suggested by the work of Katz,[13] for example, who found that half the maximum dose seemed to destroy surface spirochetes as promptly and effectively as the larger doses.[14]

My conception of the immunization technic of arsphenamin administration [15] is that of graduated, moderate dosage at safe intervals for long periods, with rest intervals designed to prevent the arsenic fastness described by Akatsu and Noguchi.[5] Moderate dosage means one-half, increasing to two-thirds, the Ehrlich maximum. A safe interval is one week. An average series or period is from six to eight injections. An average rest interval between series is from four to twelve weeks. An average number of such series is three or four.

From these two types of technic, a wide variety of combinations may be made, suited to the taste and temperament of the therapist, to his conceptions of the immunology of syphilis, to the stage of the infection, to the nature of the complications, and to the tolerance of the patient. The immunization extremist should, it seems to me, employ intramuscular administration because of the slow absorption and prolonged action thus obtained. Immunization technic, as ordinarily used in intravenous injection, enters into and explains some of the effectiveness of intraspinous therapy, of which it forms the intravenous part. It explains the nonspecific and indirect action of arsphenamin on conditions such as tuberculosis, blastomycosis, anthrax and trichinosis, in which no direct parasiticidal action is likely. Modifications of it are, to my mind, the methods best adapted to the fully entrenched and late syphilitic infection.

On the other hand, the efficiency of the spirillicidal technic in early cases is so far demonstrated that it must be given a place in general

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13. Katz, T.: Ueber intravenöse Injektionen von konzentrietem Neosalvarsan, München. med. Wchnschr. **60**:2337, 1913.

14. If for no other reason, the use of arsphenamin in syphilis should be obligatory as the only existing means of sterilizing the patient in the interest of the public health.

15. Toyama, I., and Kolmer, J. A.: The Influence of Arsphenamin and Mercuric Chlorid on Complement and Antibody Production, J. Immunol. **3**:301, 1918. (This article summarizes the experimental basis of this technic.)

syphilotherapy proportional to the earliness of the infection. In primary syphilis and in the florid eruptive stage, a massive or spirillicidal arsphenamin therapy is imperative. My personal concession to it consists of the administration of three almost maximum doses in the first nine days. To one who plans to rely entirely on a spirillicide technic, this is not intensive enough. Pollitzer's [1] three doses in three days, and Schamberg's [16] 3 dg. doses on alternate days are familiar and usually effective if properly guarded with mercury. On the other hand, I feel that no massive technic is as yet a substitute for immunity building, and I accordingly follow my single massive attack by weekly injections to the total number of eight or nine, before beginning the first arsphenamin rest interval. In early infections this should not be more than from four to six weeks, as pointed out by Gennerich, and should be protected by mercury as in shorter course technics.

COMBINATION OF MERCURY WITH ARSPHENAMIN IN SYPHILIS

The phrase "protected with mercury," discloses the cardinal weakness of the arsphenamin therapy of syphilis. The tendency to substitute arsphenamin for mercury is the blunder of the inexpert syphilotherapist. The point to be remembered is that the more massive and the shorter the arsphenamin phase is made, the less immunity or resistance is secured. Patients who have experienced nothing but the spirillicidal action of arsphenamin at the hands of an unbalanced enthusiast, are exposed to the gravest accidents, bereft as they are of physiologic defense.[18] The deficiency is to be made up to some extent by more arsphenamin. From the appreciation of this fact arose the Ehrlich aphorism "the remedy for neurorecurrence due to arsphenamin is more arsphenamin." Why more arsphenamin? Not as I conceive it, for its spirillidical effect alone, so much as for its immunity and defense stimulating qualities, brought out by the longer, more moderate dosage course.

There exists, however, ready to hand, another and even more important means than "more arsphenamin" for reinforcing the transient resistance and immunity developed by this drug. Mercury is the natural complement of a spirillicidal agent in syphilis.[19] The injunc-

16. Schamberg, J. F.: A Second Attack of Syphilis Two Years After the First; Curability of the Disease, J. A. M. A. **73**:826 (Sept. 13) 1919.

17. Gennerich: Die bisherigen Erfolge der Salvarsanbehandlung im Marinelazarett Wik, München. med. Wchnschr. **61**:513, 1914.

18. Gennerich (Footnote 17) was one of the first to call attention to this aspect of the therapy. See also Pusey, W. A.: The Present Situation in Syphilis, Am. J. M. Sc. **146**:497, 1913. Compare also Toyama and Kolmer (Footnote 15) on the inhibitory effect of large doses on agglutinin formation.

19. Compare Schreiber, Footnote 10, who discusses the complementary action of the two drugs.

tion to use it in effective form should appear on the label of every ampule of arsphenamin. In contrast to arsphenamin as a direct spirillicide in the human body, the failure of mercury has been demonstrated from a variety of angles.[20] But as an immunity stimulator it is sovereign. It must be so used in conjunction with every type of arsphenamin administration, that it fills in the gaps between the action of its more spectacular confrère with solid substantial resistance. Why not rely on it entirely? Because its action is slow when speed is most needed, and its toxicity is high, especially in prolonged administration. Arsphenamin is the broom that sweeps, mercury is the club that crushes. More than once one is impelled to wonder whether overmassive mercurialization does not wreck the patient as it "cures" the disease. Arsphenamin, on the other hand, discriminatingly employed, has a tonic action that is an inexpressible relief from the depressant action of mercury.

To secure the maximum combination of benefits, with the minimum of defects from both drugs, I believe it is essential, especially in early cases, to use them simultaneously rather than alternately. Prolonged observation of the effect of this combination has made me believe them actually synergistic in effect, and without permanent damaging effect on the excretory mechanism.[21] By simultaneous use, the slowly developed mercurial immunity overlaps the deficiencies of the transitory arsphenamin immunity, and fills the gaps between the peaks of the latter's spirillicidal efficiency. I ought to say, however, that I frankly disapprove of the routine use of insoluble mercurials such as the salicylate, gray oil, etc., in simultaneous combination with arsphenamin.[22] The leaving of mercurial depots of unknown capacity in the tissues of patients of unknown resistance and tolerance [23] in the early months of a course of treatment which may last Heaven only knows how long, is an adventure in speculative therapy that my experience

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20. Lomholt, S.: Die Zirkulation des Quecksilbers im Organismus, Arch. f. Dermat. u. Syph. **126**:1, 1918. This is an important monograph with a bibliography of 339 titles. For a discussion of the opposing views espoused by Neisser and Finger see page 65. See also Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: The Chemotherapy of Mercurial Compounds, Am. J. Syph. **1**:1, 1917. Lomholt, S., and Kissmeyer: Zur Wirkung des Quecksilbers auf Syphilis, München. med. Wchnschr. **64**:1292, 1917.

21. For the opposing view, see Loewy, A., and Wechselmann, W.: Experimentelle Untersuchungen über die Wirkung intravenöser Salvarsaninjektionen auf die Funktion der Niere insbesondere bei bestehender Quecksilberintoxikation, Berl. klin. Wchnschr. **39**:1342, 1913.

22. Pollitzer, Footnote 1, as an example of alternate use of two drugs.

23. For an analysis of this factor in the use of insoluble salts, see Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: A Study of the Comparative Toxicity of the Various Preparations of Mercury, with a Histological Study of Experimental Mercurial Nephritis, J. Cutan. Dis. **33**:819, 1915.

with the kidney in syphilis will not countenance. The 4 gm., 30 to 50 per cent. inunction and the soluble mercurial salt, as simultaneous and interim treatment, have for the past three years accomplished all I could desire of mercury in the treatment of syphilis.[24]

You will see from my high estimate of the value of prolonged maintenance of resistance in syphilis, that I have little faith in the shortened or abortive procedures which have had such vogue in cases seen in the earlier weeks or months of the infection. In the present dubious state of knowledge as to the immunity mechanism of reinfection, superinfection and so-called clinical cure, I feel that it is inexcusable to give less than from eighteen to twenty-four arsphenamin injections in an early case. These I mass into the first year, employing the spirocheticidal opening attack of three injections in nine days, as part of the first course of eight injections and from four to six weeks intervals between the later courses of six. Mucous recurrences, a test of the effectiveness of an average technic, and not uncommon after twelve unsystematic and scattered injections, have thus far never developed in my experience, in such a course, with its accompanying 300 inunctions. With inunctions given in courses of forty and eighty, and with rest intervals of one and two months overlapped by arsphenamin, it will be apparent that mercurialization extends a considerable period beyond the cessation of the arsphenamin phase.

USE OF ARSPHENAMIN IN LATE SYPHILIS

In the therapy of established or late syphilis, to my mind, the spirillicidal action of arsphenamin, while still important, and maintainable to a marked degree by reasonable dosage and interval, is no longer the paramount goal of the use of the drug. New factors enter into the case, calling for increasing individualization and greater conservatism in the assumption of treatment risks. The prospect of radical extirpation of every spirochete diminishes to the point where we must realize that the arsphenamin miracle has the odds against it. Knowledge of when to stop and observe often comes to be worth more than the rash or over-enthusiastic impulse to go ahead. In late and intrenched infections, therefore, I tend even in the absence of gross contraindications, to be more leisurely in my attack, and to extend the same course of treatment used in early infections, over a longer period, especially by increasing the interim mercurialization periods between arsphenamin

24. Hoffmann, E.: Ueber eine nach innen gerichtete Schutzfunktion der Haut (Esophylaxie) nebst Bemerkungen über die Entstehung der Paralyse, Deutsch. med. Wchnschr. **45**:1233, 1919. This author explains part of the effectiveness of inunctions by an arousing of the protective functions of the skin. See also Stokes, J. H.: Observations on the Intensive Combined Treatment of Syphilis, Mississippi Valley M. J. **25**:11, 1918. Schamberg, Footnote 16.

courses. Thus the average late interval is from four to six months between arsphenamin series, instead of the corresponding number of weeks, and the tonic action of the arsphenamin is distributed throughout the mercurialization phase, instead of being sacrificed to spirillicidal action by being massed ahead of it, as in early infections. At the same time, a decided measure of spirillicidal effect in the late infection is conserved by the massing of the groups of arsphenamin injections into compact units, insteads of scattering them by long intervals between individual injections.

In the early months of a syphilitic infection, occurring as it usually does in a young person in good general health, treatment risks are more safely taken, and routine therapeutic hammering better tolerated than in the late manifestations of the disease, when the damage done by the infection combined with the handicaps of age and the pressure of living, make the late syphilitic a less eligible subject. The therapy of late syphilis must therefore strike a balance between the gravity of the disease process and the physical handicaps of the patient. The gravity of the process must be determined by searching examination of those parts of the body whose functional integrity is necessary to life. For example, it is one of the sins of the symptomatic outlook on the disease, that a therapist, seeing the cutaneous syphilid, and knowing the ready response of such lesions to arsphenamin, administers a liberal dose of the drug, only to throw his patient into almost a cardiac fatality through his failure to consider the structural involvement of the heart, an organ necessary to life. It is equally possible to watch with enthusiasm the rapid response of an osseous lesion and to discharge the patient when it has disappeared, or to put him on minor therapy, while a neurosyphilis in the same patient, overlooked through inadequate examination, goes merrily on to an ultimately crippling and fatal outcome. Arsphenamin is capable of doing immense harm when its employment is intrusted to the spectacularly-minded, whose appreciation of its astonishing symptomatic effects blinds them to its transient action and its weaknesses. It is worth while, too, in these cases, to discourage the over-sanguine frame of mind that a limited experience with the arsphenamins is apt to develop. Remarkable as its effects undoubtedly are, it cannot restore cor bovinum, or the bulged aorta to normal, nor bring back vision to the sightless eyes in advanced simple primary optic atrophy. As an essential preliminary to all use of arsphenamin therapy in late syphilis, then, as a guide both to intensity and prognosis, I would place the complete and careful clinical and serologic examination of the entire body. Without the knowledge which such an examination gives, one proceeds about his use of the drug with only half vision if not outright blindness.

Axioms Governing Successful Use of Arsphenamin

Every user of arsphenamin in large amounts ultimately develops a group of axioms, epitomizing its applicability, limitations and contraindications for his own experience. The most servicable of these are, to my mind:

The arsphenamins are the drugs of election where there is marked renal damage, and in acute syphilitic nephritis.[25] Schamberg and his collaborators [26] have estimated its toxicity for the kidney as one fiftieth that of mercury, for example.

The liver metabolizes arsphenamin and stores arsenic.[27] Watch it therefore, to forestall accidents, and when it is structurally damaged, reduce dosage and expect lowered general tolerance of the drug.

The arsphenamins are distinctly vasculotoxic.[28] Such effects are particularly serious in vascular syphilis of the brain and in the damaged

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25. Hoffmann, E.: Ueber akute syphilitische Nierenentzündung in der Frühperiode (Nephritis syphilitica acuta praecox), Deutsch. med. Wchnschr. **39**:353, 1913. Stokes, J. H.: Acute Syphilitic Nephritis from the Standpoint of Diagnosis and Salvarsan Treatment, with Report of a Case, J. A. M. A. **66**: 1191 (April 15) 1916. Cole, H. N.: Acute Syphilis of the Kidney, Report of a Case, Am. J. Syphilis **4**:46, 1920.

26. Schamberg, Kolmer and Raiziss, Footnote 23.

27. Riebes, E.: Ueber die Verarbeitung des Salvarsans und Neosalvarsans im Organismus, Arch. f. Dermat. u. Syph. **118**:757, 1913. Stühmer, A.: Zur Topographie des Salvarsans und Neosalvarsans, Arch. f. Dermat. u. Syph. **120**: 589, 1914. The following articles voice an interesting controversy over the significance of jaundice in arsphenamin treatment. Milian, G.: Trois cas d'ictère au cours du traitement à l'arsenobenzol, leur nature syphilitique, Bull. et mém. Soc. méd. de hôp. de Paris **43**:821, 1919; abstr., J. A. M. A. **73**:1858 (Dec. 13) 1919. Deux cas d'ictère au cours du traitement par le néo-salvarsan, Paris méd. **7**:191, 1917. Sicard, Haguenau and Kudelski: Traitement de la syphilis nerveuse chronique, les éléments de contrôle de la médication novarsénicale, Bull. et mém Soc. méd. d. hôp. de Paris **43**:833, 1919.

28. Caesar, V.: Sieben Fälle von cerebralen Erkrankungen nach Salvarsanbehandlung, Dermat. Ztschr. **20**:569, 1913; abstr., J. Cutan. Dis. **32**:526, 1914. Labbé, M., and Langlois, S.: Purpura hémorragique aigu par intoxication arsénicale, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:786, 1919; abstr., J. A. M. A. **73**:1645 (Nov. 22) 1919. Pearce, L., and Brown, W. H.: Chemopathological Studies with Compounds of Arsenic. II. Histological Changes in Arsenic Kidneys, J. Exper. Med. **22**:525, 1915. The antagonistic effect of adrenalin on the vasoparetic action of arsphenamin was originally urged by Milian as explaining the efficiency of the former in hemorrhagic encephalitis due to arsphenamin. For a more recent statement of his views see: Milian, G.: (Administration of Epinephrin), Paris méd. **8**:81, 1918; abstr., J. A. M. A. **70**:1041, 1918. For recent work on the effect of arsphenamin on the adrenal, see: Hirano, N.: Experimental Studies on the Investigation of the Nature of Anaphylactoid Reactions Caused by Repeated Intravenous Injection of Salvarsan, Kitasato Arch. Exper. Med. **3**:1, 1919; abstr., J. A. M. A. **72**:1947, 1919.

myocardium,[29] and compel a greater dependence on mercury. The vasculotoxic effect seems especially marked in acute processes, and probably blends with the Herxheimer reaction.

Arsphenamin, when first administered, produces a flare-up of a syphilitic process which is proportional to the acuteness of the process and the size of the dose administered. This so-called Jarisch-Herxheimer reaction, familiar enough in the eruptive period, occurs at every stage and with varying intensity in every structure affected by syphilis. If a large dose is given in the presence of a sluggish process, or a small dose in an acute process, there will be a focal response which is of some assistance in diagnosis. On the other hand, if a large dose is given in an active process, the seriousness of the outcome will be proportional to the importance of the involved structures. Thus a manifestation intrinsically no more serious than a gummatous ulceration of the larynx may be responsible for death by asphyxiation through edema caused by a Herxheimer reaction from overdosage in an active though late process. The estimation of the acuteness or activity of a syphilitic process and the importance of the structures involved thus constitutes an important factor in determining the advisability of using arsphenamin with or without preparation, and in moderate or large dosage. Mercury, because of its slower action, should be a preliminary to the use of arsphenamin in all first courses of treatment when important structures are involved. The more acutely the nervous system in particular is affected, the longer should the mercurial preparation be. As a mercurial for preparation purposes, I prefer a soluble salt, unless there are renal contraindications or cardiac decompensation, in which case the slower inunction is desirable.

The tolerance of the arsphenamins is diminished in varying but pronounced degrees by factors which have likewise a pronounced influence in increasing the gravity of a syphilitic infection. Among these I include foci of septic infection, even if latent, which increase the susceptibility of the skin to exfoliative accidents and reduce the resistance of the kidney to therapy.[30] Acute respiratory infections and

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29. For an early experimental verification of this clinical impression see: Auer, J.: The Effect of Salvarsan on the Heart in Dogs, J. Exper. Med. **14**:248, 1911.

30. Stokes, J. H.: The Protection of the Kidney in Intensive Antisyphilitic Treatment, with Special Reference to the Influence of Dental Focal Infections, Med. Clin. North Am. **3**:82, 844, 1919. Michelson considers this in the discussion on Guy, W. H.: Reactions Following the Administration of Arsphenamin, Report of Reaction in a Series of Twenty-Five Thousand Injections, J. A. M. A. **63**:901 (Sept. 20) 1919, in which exfoliative dermatitis is reported in association with a septicemia.

influenza are apt to be exaggerated into pneumonia by arsphenamin administration.[31] Febrile conditions complicating syphilis, especially pulmonary tuberculosis which is on the down grade, usually responds unfavorably, in my experience.[32] On the other hand, if the patient's resistance is good, the response may be gratifying. Pyelonephritis and severe cystitis may sharply diminish the tolerance of arsphenamin and lead to violent febrile reactions. Urinary retention from neurogenous atonic bladders and enlarged prostates has a definite effect in retarding the progress of patients under treatment. I consider it a matter of great importance to secure a careful history of previous dermatoses, since patients who have or have had a marked dermatitis from any cause seem to me to be definitely predisposed to exfoliative dermatitis from arsphenamin, and the first injection may result in this most alarming of complications.

If due regard is paid to the necessity for a careful study of the patient before arsphenamin administration is begun, and the axioms governing its employment as I have outlined them are duly heeded, the incidental or secondary reactions to arsphenamin can be largely avoided. Primary reaction, as in the acute nitritoid crisis, arsphenamin gastro-intestinal disturbances, and the alarming and often fatal collapses recorded in the literature can be largely avoided [33] by a rigorously correct technic of administration, provided a reliable product is used. The tendency to blame either the drug or the patient for an accident should be restrained.[34] I have always felt it worth while to give the most painstaking attention to the preparation of water and of chemical reagents such as sodium hydroxid solution, to the glass, and

31. Lier, W.: Ueber Abortivkur, Spirochätenreste und kombinierte Behandlung der Syphilis, München. med. Wchnschr. **61**:2233, 2276, 1914. For an interesting exception to this rule, in pneumonia complicated by syphilis, see Head, G. D., and Seabloom, J. L.: Arsphenamin in Pneumonia with Delayed Resolution in Syphilitic Soldiers, J. A. M. A. **73**:1344 (Nov. 1) 1919. For the Production of pneumonia in connection with the administration of acid arsphenamin see: Schwendtfeger, O. M., and Tinker, M.: Pneumonia Following Injections of Arsenobenzol, Am. J. Syphilis **3**:398, 1919.

32. Potter, N. B.: Salvarsan in the Treatment of Double Infections, Tuberculosis and Syphilis, Am. J. M. Sc. **152**:823, 1916. Elliott, J. A.: The Treatment of Syphilis in Tuberculous Patients, Am. J. Syphilis **3**:291, 1919. Elliott notes especially the importance of the focal flare-up (Herxheimer). Burnham, E. A.: Syphilis of the Lung, Boston M. & S. J. **171**:411, 1914.

33. For various methods of dealing with the nitritoid crisis, see: Stokes, J. H.: Atropin and Induced Anaphylaxis as a Protection Against Acute Arsphenamin Reactions, J. A. M. A. **72**:241 (Jan. 25) 1919.

34. W. A. Pusey voices an expression of the opposite opinion in the discussion on Guy's paper (Footnote 20).

lately, as a result of the investigations of Busman and myself,[35] to the rubber tubing. The tubing reaction has special interest in showing on what subtle details the outcome of an intravenous injection of any type may depend. I am emphatically in accord with Schamberg, McCoy and others [36] in insisting on adequate dilution and slow administration of arsphenamin solutions as essential to safety. We find the hyperalkalinization [37] by a quantitative as distinguished from a visual end-point technic to produce the disodium salt in preparing arsphenamin, very serviceable.[38] The use of solutions of arsphenamin which have strong odors, unusual colors when dissolved, or turbidity when they should be clear, is dangerous, nor does the manufacturer's claim that they have passed animal toxicity tests make them fit for use in man. While it is possible to be temperamental about mild gastrointestinal reactions and unduly to modify dosage when they appear, it is worth recalling that most reactions can be done away with by the combination of correct administration with a fasting stomach and a cathartic twenty-four hours after injection.

The highly embarrassing and fatal arsenical exfoliative accidents of arsphenamin, while not absolutely preventable, can be much reduced in frequency by preliminary removal of focal infections that tend to sensitize the skin, and by watching the patient for the first sign of irritation. This usually appears in the form of more or less general pruritus, with slight patchy dermatitis in the groin, neck and axillae and about the wrists and forearms. Such scrutiny should be redoubled after the fourth injection. Inunctions should not be used during the arsphenamin courses of patients who show a marked irritability, or give a history of dermatitis. The oatmeal and soda bath and administration of alkalis such as potus imperialis and Fischer's solution per

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35. Stokes, J. H., and Busman, G. J.: Tubing as a Cause of Reaction to Intravenous Injection, Especially to Arsphenamin, Preliminary Report, J. A. M. A. **74**:1013 (April 10) 1920.

36. Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Laboratory and Clinical Studies Bearing on the Causes of the Reactions Following Intravenous Injections of Arsphenamin and Neo-Arsphenamin, Second Communication, Arch. Dermat. & Syph. **38**:235, 1920. McCoy, G. W.: The Administration of Arsphenamin, J. A. M. A. **72**:1386 (May 10) 1919. Pusey, W. A.: Administration of Arsphenamin, J. A. M. A. **72**:1786 (June 14) 1919. Young, H. McC.: The Administration of Arsphenamin, Correspondence, J. A. M. A. **73**:131 (July 12) 1919. Goldenberg, H.: The Administration of Arsphenamin, J. A. M. A. **72**:1634 (May 31) 1919. Nelken, A.: Administration of Arsphenamin, J. A. M. A. **72**:1695 (June 7) 1919. Rieger, J. B.: The Administration of Arsphenamin, J. A. M. A. **73**:710 (Aug. 30) 1919.

37. Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: (Footnote 10). Danysz (Footnote 6) Schamberg, J. F.: Caution Against the Use of Non-neutralized (Acid) Solutions of Salvarsan, J. A. M. A. **68**:1255 (April 28) 1917.

38. McCoy, Footnote 36.

rectum have seemed to me to be of value. Outright nephritis and anuria from a dose of arsphenamin has never occurred in my experience and is, I think, attributable to technical error.[39] Showers of casts are not infrequent, however, especially during epidemics of colds.

I have always been insistent on the principle of hospitalizing all arsphenamin cases until the time for most complications to develop is over, that is, for twenty-four hours. This does not protect against hemorrhagic encephalitis, which may not begin to appear for several days. On the arsphenamin service at the Mayo Clinic there have been two deaths attributable to the drug in 25,000 injections under such hospital control, among a difficult class of cases rather than among robust young adults, as in the army. One death might have been prevented had the patient been disposed to cooperate with us in the management of her focal infections. Once the operating room technic is perfected and the staff thoroughly impressed with every detail of indications and contraindications, the twenty-four hour rule may be relaxed to eight hours, if the patient is still under easy outpatient observation and can be hospitalized on the slightest sign of trouble.

USE OF ARSPHENAMIN IN NEUROSYPHILIS

Neurosyphilotherapy has furnished arsphenamin with a field for a number of its problems and for not a few of its triumphs. The frequency of neurorecurrence in the days before the appreciation of the dangers of insufficient arsphenamin, and the more or less theoretical neurotropism expected of the drug,[40] by the mistake of regarding it as a species of glorified arsenic, has led to an unwarranted distrust of its efficacy. Neurotropism in the form of polyneuritis [41] is a reportable rarity, and the greatest overdosage has not, in my experience, been followed by such complications. I have perhaps felt that simple primary optic atrophy did not do well under arsphenamin. But as for the neurorecurrences, I feel that they would all but disappear from the field, if routine examination of the spinal fluid with the last

39. Eberly, K. C.: An Unusual Case of Salvarsan Poisoning, J. A. M. A. **65**:1729 (Nov. 13) 1915. Woodyatt, R. T.: Hypertonic Salt and Alkali Solution in Salvarsan Anuria, J. A. M. A. **64**:1811 (May 29) 1915. Treatment of arsphenamin anuria with Fischer's solution.

40. For experimental evidence suggesting the minor importance of the effect of alkaline arsphenamin on nerve tissue, see Joseph, D. R.: A Few Observations on the Action of Salvarsan on the Irritability of Nerve and Muscle, J. Exper. Med. **13**:634, 1911.

41. Wolff, A., and Mulzer, P.: Zur Kasuistik der Behandlung der Syphilis mit Neosalvarsan (Arsenical Paraplegia), München. med. Wchnschr. **59**:1706, 1912.

arsphenamin injection [42] of each course were practiced. This would furnish us with sufficient warning and enable us properly to direct our treatment.[43] The rare exceptions would be those definitely neurotropic infections which respond unsatisfactorily to any treatment. It must be conceded, however, that in spite of its high value in neurosyphilis, occasional patients do not respond to the drug, and are even unfavorably affected. I have for example seen paresis in a period of remission forced into a rapid and fatal decline through ill advised arsphenamin enthusiasm. Massive mercurialization and large doses of iodids ranging from 500 to 1,000 grains daily will sometimes produce a response that no amount of arsphenamin can secure (arsenic fast organism?).[44]

I think it is no exaggeration to credit arsphenamin with having by one or another of its modes of administration reduced the mortality of parenchymatous syphilis of the brain to the point where it is no longer wise to attach an absolutely fatal prognosis to the clinical picture of paresis. In other words, only a therapeutic test with a fatal outcome now suffices to substantiate paresis as a clinical diagnosis. The redoubled arsphenamin therapeutic intensity, advocated by the late Dr. Southard and his associate Solomon,[45] has certainly in my experience transformed the clinical and serologic condition of many patients whom I would in earlier days have been disposed to abandon to their fate. Even granted that the ultimate outcome may be fatal, remissions of the most substantial kind can now be produced by intensive treatment in as high as 60 per cent. of patients who show only early signs of deterioration.

It is no longer asserted that intraspinal arsphenamin therapy, so long the center of schismatic and controversial discussion,[46] will accomplish the impossible. Rationally, it appeals to me as a local treatment of the central nervous system by combined antibody and

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42. Stokes, J. H.: Three Cases Illustrating the Diagnosis and Treatment of Syphilitic Involvement of the Nervous System, Med. Clin. North Am. **3**:829, 1919.

43. Swift advises a similar procedure in neurosyphilis under treatment: Swift, H. F.: Observations on Types of Response in Treatment of Syphilis of the Central Nervous System, Am. J. Syphilis **1**:524, 1917.

44. Stokes, J. H.: Med. Clin. North Am. **3**:836, 1920.

45. Southard, E. E., and Solomon, H. C.: Neurosyphlis, Modern Systematic Diagnosis and Treatment, Presented in One Hundred and Thirty-Seven Case Histories, Boston, Leonard, 1917.

46. From the voluminous literature on the subject, it is well to read: Fordyce, J. A.: Truth About Intraspinal Injections in Treatment of Syphilis of Nervous System, A Reply, J. A. M. A. **69**:1482 (Nov. 3) 1917. Sachs, B.: Truth About Intraspinal Injections in Treatment of Syphilis of Nervous System, J. A. M. A. **69**:681 (Sept. 1) 1917.

spirillicide agents,[47] plus a mild antibody stimulating systemic therapy. The latter element is too often overlooked in estimating the benefit produced by the intraspinal part of this procedure. The success of the localizing measure does not justify a refusal to recognize the equally enduring and substantial benefits produced by systemic treatment. My belief that syphilis must be treated as a whole, rather than in parts, leads me to deprecate a panic-stricken rush for intraspinal measures the moment a syphilitic shows signs of involvement of the nervous system. In spite of the general safety of such methods as the Swift-Ellis-Ogilvie method of treatment, intraspinal treatment involves enough risks to make it a second rather than a first choice. Much more can be done to clear up neurosyphilis by general therapy than is generally realized.[48] Adequate attention to focal infection, urinary retention, and general hygiene alone, as suggested by Duke [49] and confirmed by my own experience, will often produce a response in what threatens to be a refractory neurosyphilis. I feel that where outright contraindications are absent, every neurosyphilitic, particularly in the early years of his infection, should have at least one stiff course of arsphenamin intravenously and inunctions or soluble mercurial injections before intraspinous therapy is even considered. I have seldom attempted both procedures together.

The objection which applies to overenthusiastic estimates of the permanence of arsphenamin effects in other fields of syphilis applies to generalizations on its influence on the prognosis of neurosyphilis. Neither intraspinal nor intravenous measures will stop the drift toward an ultimately fatal outcome which some cases exhibit occasionally from the earliest weeks of the infection. Nor is the permanence of

47. I do not feel that the mechanism of intraspinal effects and the relative merits of different technics are by any means settled by the mere demonstration of arsenic in the spinal fluid in varying percentages. For important studies on this question see Ogilvie, H. S.: The Intraspinal Treatment of Syphilis of the Central Nervous System with Salvarsanized Serum of Standard Strength, Report of Cases, J. A. M. A. **63**:1936, 1914. Swift, H. F.: A Study of Serum Salvarsanized in Vitro, J. Exper. Med. **24**:373, 1916. Barbat, J. H.: Permeability of the Meninges to Arsenic in Paresis and Tabes, J. A. M. A. **70**:147, 1918. Mehrtens, H. G., and MacArthur, C. G.: Therapy of Neurosyphilis Judged by Arsenic Penetration of Meninges, Methods of Treating Neurosyphilis, Arch. Neurol. & Psychiat. **2**:369, 1919.

48. Sachs, B.: On the Intravenous, Not the Intraspinal, Use of Arsphenamin in Syphilis of the Nervous System, Arch. Neurol. & Psychiat. **1**:277, 1919. Kaliski, D. J., and Strauss, I.: On Syphilis of the Nervous System, Pathological, Serobiological and Clinical Criteria with Especial Reference to Treatment, Am. J. Syph. **2**:609, 1918. Southard and Solomon, Footnote 45. Stokes, J. H.: Med. Clin. North Am. **3**:829, 1919.

49. Duke, W. W.: Multiple Infections, A Study of the Relation of One Infection to Another, J. A. M. A. **71**:1703 (Nov. 23) 1918.

the most brilliant results yet fully assured. To my mind, however, intraspinal therapy has a unique place as an addition to general measures in resistant early neurosyphilis and as a means of local approach to a neurosyphilis which is hedged about by contraindications in the later years of the disease.[50] The symptomatic advance of serologically negative cases in spite of intensive intravenous and intraspinal therapy is a well established fact and reflects equally on the efficiency of both methods. I must, however, confess a preference in cases of this type for the immunizing effect of small doses of neo-arsphenamin intravenously rather than for the more massive procedures. Of spinal drainage, I can only say that I have abandoned it as being no more effective than intravenous arsphenamin therapy alone.

USE OF ARSPHENAMIN IN PREGNANCY AND CHILDHOOD

In syphilitic pregnancy and childhood, arsphenamin should be widely used.[51] In the pregnant woman I agree with Wechselmann [52] that conservatism in dosage is imperative, even in acute early syphilis. I seldom find it advisable to exceed from one-half to two-thirds adult dosage. The combination with mercurial inunctions seems to me to be as well tolerated as mercury alone. In childhood, arsphenamin should be pushed with the same intensity in proportion to age and weight, and under the same contraindications that apply in adult life. Rectal arsphenamin medication seems to be as complete a superfluity as mouth administration [53] to one who can master the technical difficulties in treating children. In general, syphilis acquired *in utero* should be treated by the same combination of spirillicidal and immunizing technic which I have described for late syphils in adults. The symptomatic response of interstitial keratitis to arsphenamin is vastly better than to mercury in my experience, although I realize that ophthalmologists who are not in touch with syphilographers seem to make relatively little

50. For an excellent and conservative statement of the possibilities of the method see Fordyce, Footnote 46.

51. Holt, L. E., and Brown, A.: Results with Salvarsan in Hereditary Syphilis, Am. J. Dis. Child. **6**:174, 1913. Strathy, G. S., and Campbell, G. A.: Results of Treatment with Salvarsan in Late Congenital Syphilis, Am. J. Dis. Child. **6**:187, 1913. Simpson, J. W., and Thatcher, L.: The Treatment of Congenital Syphilis by Salvarsan, Brit. M. J. **2**:534, 1913.

52. Wechselmann, W.: Kritische Bemerkungen zur Pathogenese eines "Salvarsantodesfalles," München. med. Wchnschr. **2**:1845, 1914.

53. Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: The Administration of Arsenobenzol by Mouth, J. A. M. A. **67**:1919 (Dec. 23) 1916. These authors estimate mouth administration as therapeutically of little worth. On the other hand rectal administration is advocated by Araujo, S.: Arsenical Treatment of Children by Way of the Rectum, Brazil med. **32**:234, 1918; abstr., J. A. M. A. **71**:2113 (Dec. 21) 1918.

use of the drug. There are few phases of syphilis in which the tonic effects of arsphenamin and its value as a relief from continuous mercurialization are more striking than in the syphilis of childhood.

COMPARISON RETWEEN ARSPHENAMIN AND NEO-ARSPHENAMIN

Comparisons between arsphenamin and neo-arsphenamin still rest on uncertain and ill assorted data. I think it is safe to say that in general the dose for dose superiority of arsphenamin even on a basis of arsenic equivalency (4 dg. "606" equals 6 dg. "914") is conceded by syphilographers of large experience. It is my habit to estimate seven injections of neo-arsphenamin equivalent to five of arsphenamin. The charm of simplicity in the administration of neo-arsphenamin has drawn many adherents irrespective of the abstract merits of the question. Kolmer and Yagle's [54] recent emphasis on its nonhemolytic properties deserves further study, and may explain its lower reactivity in moderate doses. Yet my own experience compels the belief that neo-arsphenamin in the past has been more tricky and vasculotropic than arsphenamin, especially in large doses. Possibly the elimination of methyl alcohol from its manufacture will correct the difficulty.[55] In the meanwhile arsphenamin commands my personal confidence where radical effects can be secured.

USE OF ARSPHENAMIN IN NONSYPHILITIC DISEASES

The therapeutic applications of arsphenamin in other diseases than the spirilloses constitute interesting applications of its nonspecific or immunity stimulating action. My personal experience extends to its employment in tuberculids,[56] in glandular tuberculosis in the absence of syphilis, in blastomycosis,[57] actinomycosis and sporotrichosis, in streptococcus septicemia [58] and in intestinal infections with lamblia [59] and endameba. The effects of the drug have been discussed in the

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54. Kolmer, J. A., and Yagle, E. M.: Hemolytic Activity of Solutions of Arsphenamin and Neo-Arsphenamin, J. A. M. A. **74**:643 (March 6) 1920.

55. Rieger, Footnote 36.

56. Ravaut, P.: L'action du néosalvarsan et la réaction de Wassermann chez des malades atteints de tuberculides diverses, Ann. de dermat. et de syph. **44**:470, 1913. Tzanck, A., and Pelbois, E.: A propos du traitement des tuberculoses cutanées et des tuberculides par le néosalvarsan, Ann. de dermat. et de syph. **45**:65, 1914. Stokes, J. H.: Clinical Studies in Cutaneous Aspects of Tuberculosis. III. The Therapeutic Management of the Tuberculids, with Special Reference to the Efficiency of Arsphenamin, Am. J. M. Sc. **157**:522, 1919.

57. First suggested to me by the late Frederick G. Harris.

58. Brechot, A.: Neo-Arsphenamin in War Surgery, Paris méd. **9**:414, 1919; abstr., J. A. M. A. **73**:232 (July 19) 1919.

59. Cade, A., and Hollande, A. C.: L'entérite à *"Giardia (Lamblia) intestinalis,"* Arch. d. mal. de l'appar. digestif. **10**:193, 1919. (This article includes the literature.)

literature [60] in the treatment of anthrax,[61] malaria,[62] pellagra,[63] filarial infections [64] and trichinosis.[65] The rationale of the action of this drug in tuberculids as studied by Nicholas, Courmont, Gate and Carlet [66] is probably similar to its effect in other nonspirillar infections. These authors found that in patients with good resistance, a marked increase in the agglutinins for tubercle bacilli could be produced by the administration of arsphenamin. If the patient's resistance were low or falling, the effect was nil or bad. The methods of administration employed by these authors were not particularly effective and the action is in all probability more pronounced by a somewhat more energetic technic. The dosage in the treatment of all the above conditions should be moderate, and persistence is essential. The indirect action of the drug makes it impossible to predict in advance either the degree or the permanence of improvement. Very striking effects, however, are frequently produced. While the results are fairly constant in tuberculids, they are much more erratic in the mycoses and in the latter the method is in my experience no substitute for the intensive use of radiotherapy and iodids. My impression of the use of arsphenamin in septicemia is unfavorable. Lamblia infections treated by the technic

60. Wadhams, S. H., and Hill, E. C.: Three Cases of Amebic Dysentery Treated with Salvarsan, J. A. M. A. **61**:385, 1913. For a very good general summary, see Best, W. H.: The Use of Salvarsan in Nonsyphilitic Diseases, J. A. M. A. **63**:375 (Aug. 1) 1914.

61. Bettmann and Labenheimer: Ueber die Wirkung des Salvarsans auf den Milzbrand, Deutsch. med. Wchnschr. **38**:349, 1912. Gsell, J. L.: Neo-Arsphenamin in Treatment of Anthrax, Cor.-Bl. f. schweiz. Aerzte **48**:1505, 1918; abstr., J. A. M. A. **72**:77 (Jan. 4) 1919.

62. Stephens, J. W. W., Yorke, W., et al.: Studies in the Treatment of Malaria. XVI. Intravenous Injections of Novarsenobillon in Simple Tertian Malaria, Ann. Trop. Med. & Parasitol. **12**:211 1918-1919. Temporary Good Effect from Single Dose, with Relapse. XXV. Arsenic in Malignant Tertian Malaria, Ann. Trop. Med. & Parasitol. **13**:75, 1919. (Unfavorable Results from Novarsenobenzol.) Reed, E. U.: Two Cases of Malaria Treated with Salvarsan, U. S. Nav. Med. Bull. **9**:278, 1915.

63. Cole, H. P., and Winthrop, G. J.: The Status of Salvarsan in Pellagra, Based on the Reports of Twenty-One Collected Cases, J. A. M. A. **56**:1794 (June 17) 1911. (Forty-nine out of seventy-two cases recovered.)

64. Deschamps, M.: Neo-Arsphenamin in Filarial Chyluria, Bull. d. l'Acad. d. méd. **81**:655 1919; abstr., J. A. M. A. **73**:230 (July 19) 1919.

65. Best, Footnote 60 (Two unfavorable reports). Van Cott, J. M., and Lintz, W.: Trichinosis, J. A. M. A. **62**:680 (Feb. 28) 1914. (Unfavorable.) McNerthney, J. B., and McNerthney, W. B.: Trichinosis: Immediate Result Following Intravenous Injection of Neosalvarsan, J. A. M. A. **67**:1086 (Oct. 7) 1916. (Favorable reprot.)

66. Nicolas, J., Courmont, P., and Gate: Production expérimentale des agglutinines chez les animaux par les injections de salvarsan, Compt. rend. Soc. de biol. **73**:245, 1912. Courmont, P., and Durand, P.: Action des lavements de salvarsan sur certaines formes de tuberculose, Lyon méd. **121**:97, 1913.

described by Cade and Hollande (small intravenous injections) respond well, often in cases which resist all other methods, and the prospect of permanence seems to be fairly good. On the other hand, relapses are not uncommon and we are not yet convinced that larger doses and longer courses contribute anything to a satisfactory result. It is possible that the effect is produced by the elimination products of arsphenamin in the intestine rather than by the intravenous action of the drug itself, although the drug by mouth seems to be without effect.[67] I have known endameba infections, which seem to be more resistant and erratic than lamblia, to relapse after twenty-six intravenous injections.

The arsenical earmarks of late arsphenamin complications and ill effects should not lead one to think of the drug as arsenic in a therapeutic sense since it is a distinctly inferior and tricky substitute. The cacodylate delusion in syphilis probably had its origin in this uncritical analogy.[68] Occasional response in sarcoids and psoriasis has been noted. In secondary anemia of syphilitic origin the response is usually good. On the other hand, an unpleasant surprise in the form of a relapse with the assumption of primary characteristcs is not infrequent, and the case runs the course of a pernicious anemia. In cases of this type it is permissible to question the Wassermann reaction on which the diagnosis is usually based, since as Sanford[69] has suggested it is possible that false positive Wassermann reactions may occur in pernicious anemia. In bona fide pernicious anemias the action of arsphenamin used as a substitute for the customary administration of arsenic, is erratic and often unsatisfactory.[70] If the hemoglobin is below 30 per cent., in my experience it is wiser to transfuse before giving arsphenamin, since the effect of the drug used in first instance is less likely to be good where the hemoglobin is below the point mentioned.

The nonspecific actions of arsphenamin must be borne in mind in employing it for therapeutic tests to determine the presence of syphilis. Herxheimer-like reactions on first injection have been known to occur in lupus vulgaris in the absence of syphilis.[71] The rapid response of some tuberculids, especially erythema induratum, combined with the fact that by some technics these cases may show partial positive Was-

67. Ravaut and Krolunitsky, quoted by Cade and Hollande (Footnote 59).

68. Cole, H. N.: A Study of Sodium Cacodylate in the Treatment of Syphilis, J. A. M. A. **67**:2012 (Dec. 30) 1916. This study effectually explodes this pernicious idea.

69. Sanford, A. H.: Diagnostic Methods in the Anemias, New York State J. M. **19**:415, 1919.

70. For a favorable report of twenty-four cases from which I doubt if a syphilitic factor has been fully excluded, see Bramwell, B.: The Treatment of Pernicious Anemia by Salvarsan and Neosalvarsan, Brit. M. J. **1**:406, 1915.

71. Herxheimer, K., and Altmann, K.: Ueber eine Reaktion tuberculöser Prozesse nach Salvarsaninjektion, Deutsch. med. Wchnschr. **37**:441, 1911.

sermann reactions, may lead to mistaken diagnoses of syphilis.[72] In malaria and anemias it is especially important to eliminate syphilis in estimating the effect of arsphenamin on the disease.

USE OF ARSPHENAMIN IN PROPHYLAXIS

No discussion of the applications of arsphenamin to therapeutics is complete without a mention of its possibilities in the prophylaxis of syphilis.[73] Where a known exposure has occurred within twenty-four hours I have employed two injections, given on successive days. The experimental aspects and possibilities deserve further study. It should be forcibly stated that such a procedure is under no circumstances to be employed later than forty-eight hours after exposure, nor is it ever to be employed in the presence of any suspected primary lesion. The use of arsphenamin for provocative procedures during the primary, Wassermann negative phase of a syphilis, or to treat genital lesions before a diagnosis is made, is attended with grave risks of confusion and complications, and should not be encouraged for general use as yet.[74]

CONSERVATISM IN USE OF ARSPHENAMIN

The last words of any discussion of the arsphenamins in therapeutics, should, I think, be an appeal for conservative interpretations. Particularly should such conservatism reign in the field of syphilis. Too short a time has elapsed since the discovery of these drugs, and too little is as yet known about the ultimate problems of the pathology, immunology and parasitology of syphilis, to justify the announcing of new infallibilities. The necropsy pathologist of the next fifty years may well, like Warthin, upset our most plausible generalizations of today. Seasoned tradition and conservatism are still the wisest guides in our interpretation of clinical cure. Arsphenamin has made it apparently possible and even probable, but only to the inexperienced has cure been made absolute and inevitable. I question, too, whether arsphenamin will prove to be the standardizer of the syphilotherapeutic field. We may prescribe minimum requirements for early cases, and if we do, let us place them, if anything, too far within the limits of conservatism. As for maximums, and for the adequate employment of arsphenamin

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72. This point is discussed with citation of the literature by Stokes, J. H.: Clinical Studies in Cutaneous Aspects of Tuberculosis. II. The diagnostic and Clinical Relations of Certain Tuberculids, Am. J. M. Sc. **147**:313, 1919.

73. Magian, A. C.: Arsphenamin Prophylaxis of Syphilis, Bull. d. l'Acad. d. méd. **81**:675, 1919; abstr., J. A. M. A. **73**:230 (July 19) 1919.

74. For the presentation in polemic form of the merits of this question, see Taege, K.: Salvarsanprophylaxe, München. med. Wchnschr. **66**:841, 1919. Riecke: Salvarsanprophylaxe, München. med. Wchnschr. **66**:969, 1919.

in difficult cases, it will be a long day before a textbook guide and rule of thumb can pilot the inexperienced through a standardized routine to a guaranteed successful result. I feel strongly that it is a major duty of all to whom circumstances have assigned the material and the facilities for such work, to provide in time, by closer observation, by follow-up and by adequate record, for the exact data on which alone can be based a final evaluation of the arsphenamins in therapeutics.

REPORT ON THE USE OF A PERMANENT SOLUTION OF ARSPHENAMIN

DUDLEY D. STETSON, M.D.
Acting Assistant Surgeon, U. S. P. H. S.; Attending Physician, New York Skin and Cancer Hospital.
NEW YORK

Since the advent of arsphenamin, we have constantly had impressed on us the necessity of using the solution immediately after its preparation. The advantages of having a stock solution ready for use at all times must be known to every one, and do not require enumeration. From the point of view of public health, such a solution is of interest, as it will extend the benefits of arsphenamin to patients in communities where it has hitherto been unavailable. For the occasional user it will also remove the dangers which arise from imperfect technic in preparing the fresh solution.

The conception of a stock solution of arsphenamin which will remain nontoxic for weeks is so at variance with our previous experience that a brief description of the method of preparation of the solution used in this trial and known as solution of Arsphenamin-Lowy, will be of interest. The arsphenamin powder as received from the various manufacturers, is first tested biologically for toxicity and is required to be of a higher degree of purity than demanded by the United States Public Health Service. The water is freshly distilled, boiled and evacuated by means of a vacuum pump. The powder is then dissolved in either hot or cold water, depending on the brand used. This solution is placed under a vacuum to remove any gases which may have been present in the powder or generated during its solution. The acidity is then determined by titration and sufficient sodium hydrate added to form the disodium salt. The solution is then again placed under a vacuum for four hours, filtered into ampules and sealed under negative pressure, the object being to obtain a solution free from air and other gases.

The clinical trial of solution of Arsphenamin-Lowy, that I report, was made in the United States Public Health Service clinic conducted in conjunction with the clinic of the department of syphilis of the New York Skin and Cancer Hospital.

The ampules received by us contained 120 c.c. of solution of a dilution of 1 dg. to 20 c.c. of water, which is the dilution used in the clinic in preparing the fresh solution. The required number of ampules were opened and the contents filtered into a large flask and the gravity apparatus filled as required from this flask. The same

method was used when handling the fresh solution. The cases were not selected, the solution being given to all patients in our customary doses of from 3 to 6 dg. to adults, and proportionately smaller doses to children. The number of consecutive doses varied from one to eight, at intervals varying from 3 to 6 days, depending on the patient's condition. A total of 850 intravenous injections were given and twenty-one intraspinal injections. The latter were given in doses of from 0.05 to 0.5 mg.

For the purposes of this trial reactions were considered to be any untoward or unusual effect occurring at the time of injection or complained of by the patient at his next visit. It is our routine custom to question each patient before treatment as to the effects of the previous treatment. In 5,819 injections of the fresh solution during the past fifteen months, there were 111 known reactions or 1.9 per cent.

In 850 injections of solution of Arsphenamin-Lowy, there were fifteen known reactions, or 1.7 per cent. Of the fifteen reactions, one patient complained of weakness after the first dose of 4 dg.; one received three doses without reaction and after the fourth dose of 4 dg. said he vomited all night and had pain in the back and headache; he received two doses of 4 dg. each, following this with no reactions; one vomited after the second dose of 4 dg., with no reaction after the next dose, which was also 4 dg.; five had headache only, with no reactions after the following doses: one had a slight diarrhea after the first dose of 3 dg., with no reactions later; one had nausea and a chill after the first dose of 3 dg., with no reactions later; one complained of dizziness after leaving the table, the dose being 5 dg.; one had a mild nitroid reaction after the second dose of 4 dg., with dizziness after the third dose of the same size and no reactions after subsequent doses of the same size; one had nausea and vomiting after the fourth dose of 5 dg., with no reactions later; one had a moderately severe nitroid reaction with vomiting after a dose of 3 dg. and gave a history of reactions after previous treatments elsewhere. There were no instances of skin eruption following the injections.

No unusual results followed the intraspinal use of the solution. A number of patients receiving intraspinal injections were treated in the dispensary and allowed to go home directly afterward.

While this test was instituted primarily to determine the toxicity of the solution for man, the various primary, secondary and tertiary lesions healed within the customary time.

One small initial lesion healed after the first dose; four others healed after from two to four doses. In one patient the macular

eruption present entirely disappeared after one dose. In one instance of maculopapular eruption the macules disappeared after the first and the papules after the third dose.

Two cases of gummatous ulcerations of the face healed after four doses, and a large leg ulcer of over a year's duration improved after the first dose and was entirely healed after five doses. During the test no other treatment was given to any of the patients.

The Hygienic Laboratory has recommended a limit of thirty days' dating on the ampules after animal experimentation, but states that "in a general way, it may be said that if the solution is kept cool there is no appreciable increase of toxicity in the course of six weeks or two months."

CONCLUSIONS

1. It is possible to prepare a solution of arsphenamin which will keep long enough to be of practical use.

2. Observation thus far shows the solution tested to have a therapeutic value, apparently equal to that of the fresh solution.

10 East Sixty-First Street.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. RAIZISS, KOLMER, ROTH, STOKES AND STETSON

Dr. William Allen Pusey, Chicago: I was greatly interested in Dr. Raiziss' account of some of the faults of arsphenamin, and I admire the brave statement of the facts from him, a worker in the production of arsphenamin, that many of the troubles we get in the therapeutic use of the drug come from the drug itself. When a man dies from poison, like that of arsenic, after taking a dose of arsphenamin, it always does violence to my reason to have it emphasized that he must have died of some other cause, which has always been regarded as innocent and was never known to kill anybody before. It is highly interesting, therefore, to have Dr. Raiziss meet the issue squarely and tell us the damages he has found experimentally that arsphenamin produces.

While he showed from the experimental use of large doses in animals that arsphenamin itself has its potent dangers, Dr. Kolmer's paper supplements that of Dr. Raiziss in striking fashion by showing that many of the accidents from arsphenamin arise from changes in the drug due to manipulations or faults in technic in its administration, and thus we who administer it have responsibilities quite as heavy as are those of the manufacturer. He does not undertake to show that mishaps are invariably the fault of the physician, as some of the commercial exploiters of the drug would have it. He shows that the most common damage occurs in the kidneys and liver, and this confirms my impression. I was surprised to find that he did not find the damage in the meninges that we have learned to dread through the occurrence of hemorrhagic meningitis. I have come to the conclusion that the chief danger of arsphenamin in practical use is the danger to the kidneys. The only cases I can recall in which I fear I have done the patient actual harm have been those in which there has been the production of nephritis.

As to the comparative dangers of mercury and arsphenamin to the kidneys: On the basis of a purely clinical experience I cannot subscribe to the view that arsphenamin has less danger to the kidney than mercury. In my experience the therapeutic use of mercury pushed vigorously has shown little tendency to damage the kidney, whereas arsphenamin has shown considerable tendency to damage. I am familiar with the oft quoted statement that mercury has been found to be fifty times as poisonous to the kidney as arsphenamin, and I am ready to believe that 4 dg. of mercuric chlorid would be fifty times as dangerous to the kidney as 4 dg. of arsphenamin. It would certainly be dangerous enough. But we do not give mercuric chlorid in 4 dg. doses, and used in the doses that it is used, I am not able to subscribe to the claims of its great danger to the kidney.

I enjoyed Dr. Stokes' paper very much. In a general way I accept his creed. I am, however, not such a high churchman as he is, and my ritual is not so elaborate. I think he has given an excellent exposition of the therapeutic use of arsphenamin and one that accords with conservative judgment and experience.

Dr. William H. Guy, Pittsburgh: Since the introduction of the arsenicals a voluminous literature has grown up, but nothing more important has been presented at any one time than we have heard today. In the application of any therapeutic agent an attempt is made to obtain a therapeutic victory with as little damage to the patient as possible, and the way is paved to success along those lines when facts displace theory and conjecture regarding the use and limitations of any drug. In Dr. Raiziss' paper the question of the toxicity bearing on the impurities is interesting because of the fact that he has arrived at some conclusions, as yet indefinite, that there must be some small impurity, such as was reported by Drs. Schamberg, Raiziss and Kolmer before. I think most of us will agree that certain lots of the drug are more toxic than others, and that it is very difficult to account for the reactions except by the content in the drug of some unknown impurity.

The paper of Dr. Kolmer is interesting because of the fact that while it shows very definite pathology in the dosage given, it also demonstrates that in doses ordinarily used therapeutically, while not free from danger, arsphenamin is comparatively safe. The relative toxicity of acid, monosodium and disodium arsphenamin is clearly demonstrated. It behooves us to use a technic that will avoid the pitfalls pointed out.

Dr. Roth's paper raises the question of foreign and American products, and it is very gratifying to know that we can manufacture a product far superior to any foreign product.

What constitutes immunity in syphilis is a difficult question. I believe it is fair to say that the only real immunity in syphilis is that conferred by an uncured infection. If any real immunity is created following a cure in syphilis, it certainly is short lived.

Dr. Elliott's conclusions agree with clinical experience. His reference to the reactions reported in connection with my experience in the army leads me to say that I cannot definitely state whether or not new tubing was responsible. Certainly, the fact that Dr. Stokes' clinical picture agrees so closely with mine makes it suggestive. The one thing that was found at the time was the fact that a new still had been installed with lead and copper lining. The fact as shown by Emery that arsphenamin is increased in toxicity by these two metals we thought to be significant. The use of a standard preparation of arsphenamin has its advantages for the man who is far from the beaten paths because it

relieves him of many ordinary difficulties. Against it is the fact that most of us do not have need of it and that most of the technical difficulties are overestimated; also there is greater expense in using the drug in that manner.

Dr. Richard L. Sutton, Kansas City, Mo.: In all cases of syphilis we must study the patient as well as his disease. We must build up his resistance to the highest possible point. I have repeatedly seen cases in which it was apparently impossible to secure a negative serum test promptly become negative following the removal of some concomitant focal infection, or following a good physical and mental rest. While the remedy is not a specific in pemphigus, I have had excellent results following its use in several instances, especially when injected intramuscularly, so that the patient will secure the benefit of prolonged arsenical medication. In dermatitis herpetiformis, lichen planus and psoriasis, arsphenamin has proved of little or no value in my hands. It is extremely simple to prepare a solution of arsphenamin. An intelligent nurse can learn how to do it in about twenty minutes. I feel that any physician who has not skill enough or initiative enough, or sense enough to mix his own preparations had better leave so powerful a drug alone.

Dr. Augustus Ravogli, Cincinnati: Many physicians begin with intravenous injections of arsphenamin in 0.2 or 0.4 dg. doses, giving one injection per week. I do just the reverse. I begin with 0.6 dg. and give three injections of 0.6 dg. each every two or three weeks and then I reduce the dose. I think the best way is to give a large dose in the beginning and then decrease. In a very few days the hard chancre melts away. I have never had any untoward effect. I never use gray oil more than once a week, from 6 to 8 minims at each injection.

Dr. Ernest L. McEwen, Chicago: I was glad to hear Dr. Roth speak about the danger of shaking the solution of neo-arsphenamin. Reasoning from the statements that are made relative to oxidization of this product, I have always felt there must be some danger in agitation to effect solution, but I never could get any authoritative information on the point. Having had a very bad reaction from a certain make of neo-arsphenamin, I wrote the manufacturers asking them how much danger there was in shaking to bring the powder into solution. They replied that with a short period of agitation there was no danger, but prolonged shaking might produce harmful changes. I also asked them how much danger there was in leaving the solution exposed while preparing the patient; they replied that under ordinary conditions half an hour was perfectly safe. In a case of oriental sore, two doses of arsphenamin were given without any effect whatever.

Dr. Charles M. Williams, New York: I agree that it is essential to make a positive laboratory diagnosis of any sore before starting treatment, but in some cases it is not as essential to do this as to get the man cleaned up. In some instances, as in army camps, large bodies of men are removed from laboratories and microscopes and other necessary equipment, and the important thing is to get them cleaned up. I believe, therefore, that there are exceptions when one is justified in beginning the treatment at once in cases in which the diagnosis is based on clinical findings only.

Dr. George W. McCoy, Washington, D. C.: Were the toxic results reported from arsphenamin of commerce or from rejected lots? In other words, had they passed through the hygienic laboratory test or did they represent something else. With respect to foreign products, I am sure it is not very generally understood that arsphenamin and neo-arsphenamin may not be imported or sold or manufactured in the United States, except in establishments having

a government license. Recently, several establishments abroad asked for licenses, and we have a man in Europe now who is investigating these establishments, and if they are found to meet the standard, a license will be granted. The failure to do this before has had no great influence, for, as the papers presented here have shown, there is plenty of high grade arsphenamin in the United States. If the United States grants licenses, there is still a question whether producers in foreign countries would have a right to ship these arsenicals into this country because the patents for all these preparations have been sold to a corporation, the Chemical Foundation. The best legal information seems to indicate that the rights of the Chemical Foundation to those patents are valid.

In relation to the quality of the drug of American make: More than two years ago we began to get reports from the venereal disease clinics, covering thousands of cases every year, and it has come out definitely that the reactions from arsphenamin and neo-arsphenamin were almost invariably associated with improper technic of administration. You might be surprised to find how often arsphenamin is given without adequate dilution and how often the dose is injected into a vein in from thirty to sixty seconds. Another thing is that hot water is required for the preparation from one American laboratory, while to use hot water with other American preparations increases the toxicity very decidedly. All the instructions that go with these latter preparations warn against using hot water, and yet frequently we have had reports of bad results from that.

In respect to arsphenamin in solution, I hold no brief for it. When the matter was brought to our attention several months ago, I thought considerable risk was involved. We consulted pharmacologisst and chemists as to the advisability of issuing a license for anything of that sort. Then we got the producer to come to the Hygienic laboratory and demonstrate the method of manufacture, and after much consideration it was felt that so far as we could determine the preparation was, at least, relatively free from risk and a proper one for license.

Dr. Harold N. Cole, Cleveland: I disagree with Dr. Williams. I think it inadvisable for this Section to go on record as advising any general practitioner to treat any sore until a diagnosis of syphilis has been made. I agree with Dr. Sutton that the man who cannot mix his arsphenamin or neo-arsphenamin should not give it. He has no right to do so. Too many cases of syphilis are being treated by men who have no right to treat syphilis, and the results will show in the next generation.

Dr. Julius Grinker, Chicago: I have used concentrated solutions of neo-arsphenamin hundreds of times in cases of nervous syphilis. I have shaken the bottles and I have yet to see a bad reaction, except those we see occasionally. I see no difference in the effect between concentrated and diluted solutions. As regards arsphenamin in permanent solution, I have had an opportunity of trying about sixty or seventy ampules of this preparation at the Cook County Hospital, and neither I nor my interns have been able to report a single bad reaction. I am convinced, therefore, that those who have no means of preparing the arsphenamin or neo-arsphenamin can now treat syphilis. I cannot help but disagree with Dr. Sutton; because a man cannot take out a tumor of the brain does not mean that he cannot diagnose a tumor of the brain and direct its removal, and that because a man cannot give an injection which a trained nurse can give, he has no right to treat syphilis. If a solution is handed to

him for the treatment of syphilis, and that solution has been proved to be without risk, there is no reason why he should not use it for the benefit of his patient.

Dr. Alec N. Thomson, Brooklyn: From the viewpoint of the propagandist who is endeavoring to get better treatment and earlier diagnosis for the syphilitic patient through the medium of the general practitioner, I think we should emphasize what Dr. Grinker, Dr. Cole and Dr. Williams said. This information should be placed before the entire medical profession in an effort to get better diagnosis and earlier treatment.

Dr. J. N. Roussel, New Orleans: I wish to call attention to the wonderfully beneficial effect of arsphenamin in the treatment of plantar warts. I have warts treated ineffectively, recur and disappear within ten days after one 0.4 dg. dose of neo-arsphenamin.

Dr. Marion H. Foster, Alexandria, La.: One should never agitate arsphenamin vigorously while mixing. Reactions will follow if it is done. After giving about 1,800 injections, I have concluded that neo-arsphenamin is not nearly as reliable in the treatment of syphilis as arsphenamin, and I do not use the former if the latter is obtainable. Nothing has been mentioned concerning the complete rational treatment of syphilis, which, of course, includes more than medication by arsenic alone. Although it is the great spirocheticide, arsphenamin cannot become operative against organisms buried in massed indurations until these areas are sufficiently obliterated by the use of iodin to tolerance, and this influence is just as essential for the induration of the primary chancre as it is in indurations of the later stages, for the reason that the pathology of obliterative endarteritis is common to all.

Dr. Otto Lowy, Newark, N. J.: As the man responsible for solution arsphenamin-Lowy, I take exception to some of the statements made, namely: That the physician who cannot prepare an arsphenamin solution has no business to treat syphilis. This statement would be all right if medical colleges and state boards of licensure would insist that medical graduates cannot practice medicine until they are fully qualified to prepare these solutions properly. Furthermore, as long as older physicians, who have neither the facilities nor the experience to prepare arsphenamin solutions, are permitted to practice medicine, the dictum laid down by Dr. Sutton and others cannot hold. It is all right for the gentlemen who have all the proper facilities, such as nurses, stills, time, etc., at their disposal to say that they do not need a ready made solution, but how about the country practitioner? Is his patient to be permitted to infect the entire community because he cannot mix arsphenamin and therefore should not be permitted to treat the infected individual? Or would it be better to have the doctor go to the roundhouse to take the water from the exhaust of the locomotive or to the icehouse to receive his distilled water? Solution arsphenamin-Lowy has not been prepared to popularize the treatment of syphilis, but to put into the hands of qualified practitioners of medicine a safe solution of arsphenamin.

Dr. M. J. Farber, St. Joseph, Mo.: Shall a country practitioner who has no familiarity with the technic of administration of these drugs be barred from administering them? Is it the toxicity of the drug that makes it impossible? Or is it the administration of the drug by an improper method? If a patient is killed by improper methods, by unhygienic technic, or undistilled water, shall we put the fault on the manufacturer of the drug, or lay it to the unskilled administration of the drug? Shall we today indiscriminately administer the

drug before finding out if the disease is syphilis? Or whether a primary sore is a chancre or not? We should install in every city, town and village a society for the prevention of social diseases to which a patient can be sent for a diagnosis. Dr. Sutton is right in saying that the man who cannot prepare his own solution of arsphenamin or neo-arsphenamin should not meddle with it. If he does not know the dose of a toxic drug, surely he is not going to administer that drug before inquiring what the dose is and how it should be administered.

Dr. Arthur W. Stillians, Chicago: I suggest that Dr. Reasoner add tuberculid to the list of nonspecific diseases that can be treated very successfully with arsphenamin. I have seen some very excellent results in cases that had resisted other methods. I wish Dr. Stokes would tell us what his objection is to the alternation of arsphenamin and mercurial treatment.

Dr. W. D. Calvin, Fort Wayne, Ind.: A man who cannot make a venepuncture or who cannot learn how to administer arsphenamin had better have his diploma revoked. I object to some of the views expressed by some of the speakers because of the reflection on the general profession. I can conceive of men so situated that it is not easy to prepare these solutions. If the manufacturers have arrived at that accuracy so that a preparation of arsphenamin can be prepared in a form that is not objectionable, I think I will use this preparation in the future, although, as a rule, I mix my own preparation. If it is true that so many of the population are syphilitic, as has been stated today, and we must rely on those who are expert in administering this treatment, we will have a large percentage of the syphilitics going untreated. That would be decidedly unfair. Therefore we should be more lenient in our criticisms of the preparation of solutions by the manufacturer.

Dr. Walter J. Highman, New York: I was much interested in Dr. Reasoner's paper, particularly in connection with ratbite fever, a disease which should be known by the dermatologist, for some of its features suggest erythema perstans. I am not surprised that Dr. Reasoner has not mentioned pemphigus. I have seen many cases and arsphenamin, as all other therapy, has been useless. In regard to plantar warts, I wonder whether Dr. Roussel made a Wassermann test in those cases in which the warts so rapidly disappeared after arsphenamin was given. However, the most important questions are those of arsphenamin reactions, and the use of permanent solutions. In at least two instances, I think that death might have been unjustly ascribed to arsphenamin.

In regard to the permanent solution of arsphenamin, Dr. Calvin has so completely expressed my views that there is little for me to add. I do not take the attitude of Dr. Sutton, but think that whenever anything of this sort comes into existence we should, at least, try it before condemning it, because the only hope of eliminating syphilis is to make its management easy. If 8 per cent. of our population are syphilitic, as has been brought out, and I think it is nearer 18 per cent., we have not trained syphilographers enough to meet the demand. Unless some one comes to the rescue and simplifies therapy, we will not be able to treat syphilis in bulk, and the social problem of treating syphilis is to inundate syphilitics with arsphenamin, as well as mercury. A permanent solution of arsphenamin will aid in this campaign.

Dr. Paul E. Bechet, New York: It might be possible that toxicity is increased either by the concentrated (from 5 to 10 c.c.) hand syringe method, or the use of dilutions of 120 c.c. and over. The natural tendency with the hand syringe is to give the injection too rapidly. It seems plausible that rapidity of injection plus concentration would tend to increase accidents. On the other hand, excessive dilutions increase the so called "water faults." In my experi-

ence, reactions are greater with overdilution or concentration than with dilutions of from 60 to 80 c.c. to a full dose, given by the gravity method. Since adopting this dilution, with the usual other precautions rigidly observed, I have not had a single reaction, slight or otherwise, for the preceding two years.

Dr. George P. Lingenfelter, Denver: Is the arsphenamin solution mentioned really permanent? My understanding is that it is supposed to last only about four weeks.

Dr. Cary Eggleston, New York: While I am generally opposed to embracing new products and recognize the fact that there is often an excess of enthusiasm on the part of their manufacturers, nevertheless, looking at it from the point of view of the man who does not devote his entire time to dermatology and syphilography, I feel that, perhaps, there is need for a well prepared, easily administered solution of arsphenamin. In the rural districts and small towns where skilled syphilographers are not present, it seems to me that we should encourage the physicians who are there to handle syphilis to the best of their ability, and that we should make their usefulness as great as possible by relieving them from more or less difficult technical matters. We should encourage their use of arsphenamin and thereby increase the effectiveness of the treatment of syphilis. It has seemed to me that the criticisms have been made from the personal point of view; that is, the viewpoint of the man with the well equipped laboratory who is administering a large amount of arsphenamin every day, and not from the point of view of the man who occasionally treats syphilis under unfavorable circumstances. If a commercially prepared stable solution of arsphenamin is shown to be without danger, I, for one, believe we should urge its use and lend it our support.

Dr. W. T. Watson, Baltimore: I do not live "on the frontier," but yet this prepared solution appeals to me very much from the point of view of saving my time. I can get freshly distilled water, and I have no trouble whatever with my technic, but it is time consuming and I am always hunting for ways of saving time.

Dr. George W. Raiziss, Philadelphia: I was glad that Dr. Pusey appreciated the position we had taken in reference to the search for truth as far as arsphenamin is concerned. Much has been written on the pathology and clinical experience with arsphenamin and neo-arsphenamin, but little is known of the chemical composition of these drugs. How close to the theoretical formula is the drug as used in practice today? Dr. Guy mentioned the indefiniteness of the results. The results are definite, but the work is not yet complete. I found that in order to appreciate the composition of arsphenamin, we must not be satisfied only with the official requirements of arsenic analysis. Other elements must be sought for. I found definitely that as far as the relationship of the arseno group to the amino group is concerned, we are dealing with an exceptionally pure compound. The same cannot be said of neo-arsphenamin. It is surprising to find that so little is known of the chemistry of neo-arsphenamin. Experience has shown that shaking the water solution of arsphenamin before the addition of alkali produces but very little oxidization. I have always emphasized the undesirability of unnecessary exposure of the alkalinized solution of the drug to air.

Dr. John A. Kolmer, Philadelphia: While necropsy reports indicate the production of serous and hemorrhagic meningitis in Europe, in this country meningeal changes have been much less conspicuous and generally absent. Our experimental animals frequently showed congestion of the meninges and

some intracerebral hemorrhages, particularly after the injection of acid solutions and to a lesser extent after alkaline solutions, but the American made arsphenamin does not appear to produce the meningeal and cerebral changes reported in fatal cases in Europe. All of our studies were made with arsphenamin and neo-arsphenamin that had passed the official toxicity tests, namely, 100 mg. per kilo of arsphenamin and 200 mg. per kilo of neo-arsphenamin. I wish to emphasize the practical and important relation of concentration of solution of arsphenamin on the results of toxicity tests. In our early tests we were accustomed to inject rats and rabbits with a piston syringe, and following a natural tendency when using a syringe the injections were made rather rapidly. Under these circumstances arsphenamin was considered satisfactory if an animal survived 50 or 80 mg. per kilo. When we began injecting rats with a gravity apparatus, we found that tolerance was appreciably higher. I am absolutely convinced that the rapid injection of concentrated solutions of arsphenamin increases the percentage of reactions and that the diluted form is preferable for administration to persons. Dr. Schamberg, Dr. Raiziss and I have compared the two compounds by extensive series of trypanocidal tests, employing rats. The microparasite used was a strain of *T. equiperdum* that is fatal for white rats in about six days. To prevent trypanosomiasis and save the life of the animal it is necessary to administer about 20 mg. per kilo of body weight of arsphenamin; to accomplish the same with neoarsphenamin it is necessary to inject about 40 mg. per kilo of body weight. Insofar as these trypanocidal tests are concerned, arsphenamin has about one and three-quarter times the therapeutic effect of neoarsphenamin and we cannot really say that 0.9 gm. of neo-arsphenamin is equivalent in therapeutic activity to 0.6 gm. of arsphenamin. Relative to the toxicity of the two drugs, they have varied considerably in our laboratory. About six months ago Dr. Schamberg, Dr. Raiziss and I conducted a large series of comparative tests with arsphenamin from six laboratories, finding that they varied in toxicity for rats in doses ranging from 80 to 140 mg. per kilo. The general average was 105 mg. per kilo. With neo-arsphenamin the results were from 180 to 300 mg. or more per kilo of body weight. The general average was about 254 mg. per kilo. Neo-arsphenamin therefore, is much less toxic than arsphenamin, and I believe should be given in larger doses than customary, or, at least should be given at shorter intervals in order to obtain the same therapeutic effects secured from arsphenamin. In regard to the dilution of neo-arsphenamin, my remarks referred only to arsphenamin. So far as I know, 0.9 gm. of neo-arsphenamin may be administered dissolved in from 5 to 10 c.c. of water with safety and satisfactory results.

Dr. George B. Roth, Washington, D. C.: Too little attention is paid to the relative instability of neo-arsphenamin and arsphenamin. I have commonly observed that the various preparations vary greatly in their toxicity. One may have a minimal lethal dose of 180 mg. and another of 80 mg. per kilo. Now if we take a high grade arsphenamin and mistreat it by shaking, for instance, we are bound to get bad results on administration. However, high grade arsphenamin should stand more mistreatment than a relatively low grade product. Original toxicity as well as decomposition must both be considered when we talk about the impurities of arsphenamin. I want to emphasize the fact that neo-arsphenamin, especially, is a very unstable substance and when shaken as an aqueous solution, in the presence of air, it becomes highly toxic, presumably from the formation of "arsenoxid." Some lots of neo-arsphenamin seem to be especially "sensitive" and become toxic more readily than others. Some speakers have credited me with saying that neo-arsphenamin should be

discarded. The statement I made was, that relatively difficultly soluble neo-arsphenamin should be discarded. This conclusion was reached because, in our experience, such preparations killed about 90 per cent. of the animals, and so we look on difficultly soluble neo-arsphenamins as very dangerous products.

Dr. John H. Stokes, Rochester, Minn.: I have always felt that the kidney was the most abused and least appreciated factor in the treatment of syphilis. I think we have made 30,000 examinations of the urine, many blood urea examinations and renal function tests, and I have yet to see satisfactory evidence that arsphenamin is more toxic to the kidney than mercury. Indeed, I have seen every evidence that the reverse is the case. Schamberg, Raiziss and Kolmer have also estimated that the toxicity of mercury is about fifty times that of arsphenamin. Dr. Elliott's work follows the logical approach to the question of arsphenamin effects. In both the one injection and two injection a week method of giving arsphenamin there was very little evidence that the kidney was at all affected. It is a misfortune to have to use such a word as "immunize." We know very little about the nature of resistance to syphilis, although agglutinins for the *Spirochaeta pallida* are known. In regard to Dr. Foster's comment on neo-arsphenamin, there are not sufficient data on which to base a true idea of its clinical value. I depend on arsphenamin for radical results. I disagree emphatically with Dr. Williams. The practices of military life should not be transferred root, stalk and branch to the conditions of civil life. It would be a misfortune if word should go forth from this section that early lesions should be treated on sight and without careful diagnosis. You will find a polemic in the *Münchener Medizinische Wochenschrift* in which every side of the question is discussed. As to Dr. Stillians' question, I see no objection whatever to the alternate use of mercury and arsphenamin in suitable dosage. I simply stated that I thought it advisable in the earlier stage of the infection to use them synchronously, but that later in the disease I used them alternately.

Regarding Dr. Lowy's preparation, I want to congratulate him for the way he has brought it to the attention of the profession. After testing 500 doses of the solution I must say that I do not like it as well as the preparation we make ourselves on the spot. It seems to be more alkaline and to produce thrombosis quite a good deal oftener, and this is important in a one vein arm. I feel, too, that it produces more gastro-intestinal reactions than freshly prepared arsphenamin. I feel that it will deservedly have great vogue and I hope that Dr. Lowy will carry through his entire sales organization, to the very last man, the high principle which he has put into its introduction to the medical profession. I know that it has been proposed as a selling argument for such a preparation that it will make it unnecessary for the general practitioner to use the judgment of experts. I do not think it should be sold as a means of keeping syphilitics out of the hands of experts, but that it should be a means of enabling the expert to extend his influence to the farthest point of the field, by securing better technical cooperation from the average physician. Dr. Nichols, have you had any experience with the use of arsphenamin in sprue?

Dr. Dudley D. Stetson, New York: It is not within my province to argue either for or against this solution. It is well known that many physicians are using various substitutes for arsphenamin simply because these substitutes come to them in ampules ready for injection. If instead of doing this they can be brought to use arsphenamin, a world of good will be accomplished. As to the keeping qualities, the Hygienic Laboratory has placed a limit of thirty days on the solution, and this limit should be observed. I have used a few ampules

kept for six weeks at room temperature with no bad results, but this is not recommended. Dr. Lowy informs me that he has kept the solution in a refrigerator for six weeks and found that it would still pass the required test for toxicity.

Dr. Henry J. Nichols, Washington, D. C.: In the treatment of plantar warts we have had no experience and are not familiar with any other references. If arsphenamin is so efficient, and if warts are infectious, it is possible that they may be due to spirochetes, or the Wassermann reaction may have been positive in these cases. We have a number of cases of sprue, and arsphenamin has been used, but not systematically. The results of sporadic use have not been encouraging.

We overlooked pemphigus. I recall a number of references in the older literature, but had not seen anything recently on it. The point we wished to emphasize was the group action of arsphenamin in spirochetal diseases. In spite of the "advanced state of our knowledge," we have a subconscious feeling that syphilis is a peculiar disease. However, from a conscious point of view, we know that treponema pallidum is not essentially different from any other pathogenic micro-organism, and the sooner we overcome our subconscious attitude and realize that syphilis is an infectious disease just like any other, the better we will be qualified to treat it. This point of view is reached by considering syphilis as one of a group of spirochetal diseases. Another subconscious idea we have is that arsphenamin has a peculiar effect on *Spirochaeta pallida*. This idea is also a mistaken one, because in the beginning Ehrlich worked with a group of four diseases due to spirochetes—relapsing fever, fowl spirochetosis, yaws and syphilis—and more nearly succeeded in curing the other three of these diseases with a single dose than he did syphilis. There is something to learn about arsphenamin, therefore, in considering its effect on diseases due to other spirochetes than *Spirochaeta pallida*. If I may be permitted to summarize the discussion, I would emphasize the following points: First, in regard to reactions, there have always been some complications in the use of arsphenamin. From today's symposium it is clear that the drug itself may be at fault, and that we must demand a high standard of purity. Also, it is evident that the tissues may be damaged even by a pure product under certain circumstances. The man who is giving the drug has much responsibility in regard to reactions, and the following rules must be observed: (1) arsphenamin must be made alkaline beyond the point of solution of the neutral salt so that the disodium salt is formed; (2) it must be diluted properly; and (3) it must be given slowly, and must not be shaken after it is in solution. Finally, a number of points about the therapeutic plan and the individual patient must be considered. When all of these possibilities are provided for, we can and do obtain wonderful and brilliant results.

In regard to the relative value of arsphenamin and neo-arsphenmanin: Neoarsphenamin is easier to give, and possibly less toxic, but it has not the punch of arsphenamin, either in clinical or serologic results. However, manufacturers are making about seven times as much neo-arsphenamin as arsphenamin. This means that there is a demand for a drug which is easier to give. If it is true that arsphenamin is the best drug, there is some justification for the trial of the Lowy preparation. This preparation has been licensed by the Hygienic Laboratory, and it should be given a trial. In regard to the criticism that drugs should be prepared only by the man who is going to use them, I venture to say that there are a number of men who give vaccines and serums without

knowing any more about them than the man who uses the Lowy preparation knows about that. Undoubtedly syphilis is best handled by persons who understand and can control the technic of arsphenamin preparation, but there may be a certain field for arsphenamin solution ready for use. I am particularly interested in arsphenamin because I gave the first dose given in the United States, in the Spring of 1910, at the Rockefeller Institute, and I have worked on the subject more or less ever since. The last ten years have seen a great improvement in the method of handling syphilis by American practitioners, and they have also contributed a great deal to the elucidation of the proper use of arsphenamin.

POLYNEURITIS PLUS DERMATITIS EXFOLIATIVA FOLLOWING NEO-ARSPHENAMIN *

B. BARKER BEESON, M.D.
Assistant Professor of Dermatology and Syphilology, Chicago Policlinic; Attending Dermatologist, House of Correction and Policlinic Hospitals
CHICAGO

The list of phenomena which have been observed following the administration of arsphenamin and neo-arsphenamin is a lengthy one. I shall not attempt to add anything new to this subject, but I wish to emphasize a syndrome the rarity of which is attested to by a review of the literature as well as in personal communications from a number of syphilographers.

To attempt to deal adequately with both polyneuritis and exfoliative dermatitis would be, I believe, too great a task for a paper of this character. For the sake of brevity, because of its infrequency and also in order to give it deserved prominence, I shall therefore confine myself almost wholly to a discussion of polyneuritis. I shall refer not only to cases following the use of arsphenamin and neo-arsphenamin, but I shall mention also other instances due to arsenic, as well as to syphilis and mercury.

CASES OF ARSENIC POLYNEURITIS REPORTED IN THE LITERATURE

The association of polyneuritis and dermatitis exfoliativa following the arsenical preparations just referred to was first mentioned by Duhot [1] in 1912. In patients treated according to Schreiber's technic using large doses of neo-arsphenamin, 1.2 to 1.5 gm. repeated every two or three days until four or five injections had been given, he observed the following syndrome: At first the patients complained of formication and pain in the soles and calves. The feet and legs became edematous, the skin reddened and a furfuraceous scaling appeared. When the trouble was of a more serious nature the successive disappearance of the plantar, Achilles and patellar reflexes was noted. There were cramps in the calves associated with a loss of muscular power in the legs and even paralysis. Similar but less

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1. Duhot: Etude préliminaire et expérimentale sur le neosalvarsan ou préparation neutre de 606, Rev. belge Urol. et de Dermato-Syph. **1**:91, 1912.

marked symptoms appeared in the hands and arms. There was no evidence of rectal or vesical disturbance. Duhot saw five cases of this kind and believed them all to be due to chronic arsenical intoxication. None of his patients showed evidences of cerebral involvement or disorders of sight or hearing. The nervous symptoms appeared from two to three weeks after the completion of the treatment. Later Duhot emphasized the importance of an examination of the reflexes before inaugurating neo-arsphenamin treatment. In over 1,200 patients, to whom about 9,000 injections of arsphenamin were given, he saw no such nervous symptoms. Both Ehrlich and Wechselmann [2] at an early date emphasized arsenical neuritis following neo-arsphenamin treatment.

Spillmann [3] reported a case of scarlatiniform erythema plus polyneuritis following two injections of neo-arsphenamin given ten days apart. The first injection, 0.40 gm., was followed by fever, headache and diarrhea. Two hours after the second injection (0.3 gm.) the patient became violently ill, exhibiting high fever, pulse of 150 to 160, severe headache, diarrhea and other symptoms. The erythema appeared next day and soon spread over the entire body. Symptoms of polyneuritis appeared in the legs five weeks later and were soon followed by paralysis of the left facial nerve.

Latham [4] and Carr [5] have recently reported in our literature fatal cases of dermatitis exfoliativa after arsphenamin treatment. In a personal communication, Dr. Fordyce has mentioned a case analogous to ours, which he saw in consultation. It was an exfoliative dermatitis following arsphenamin treatment in which multiple neuritis appeared about six weeks after the dermatitis had cleared up. Drs. Ormsby and Howard Morrow also informed us that they had observed examples of this syndrome. Drs. Charles J. White, S. E. Sweitzer, Everett S. Lain and Udo J. Wile have observed polyneuritis following these drugs. Dr. Shelmire has seen a patient in consultation who presented exfoliation of the skin plus icterus and a generalized purpura following two arsphenamin injections. It appears that exfoliative dermatitis has been observed by a large majority of those whose experience with these preparations has been extensive.

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2. Wechselmann: Ueber Neosalvarsan, München. med. Wchnschr. **59**: 2099, 1912.

3. Spillmann, L.: Un cas d'intoxication arsenicale suraigue à la suite de deux injections de Neosalvarsan, Bull. Soc. franç. de dermat. et syph. 100, 1914.

4. Latham, J. R.: Exfoliative Dermatitis Due to Arsphenamin. Report of a Fatal Case, J. A. M. A. **73**:14 (July 15) 1919.

5. Carr: Exfoliative Dermatitis Following the Administration of Salvarsan, Proc. Med. Assn. Isthmian Canal Zone **10**:115, 1917.

Brooks and Roberts [6] have thoroughly described the cutaneous manifestations following the epidemic of arsenical beer poisoning in England during 1901. The symptoms observed corresponded closely to those seen after arsphenamin and neo-arsphenamin treatment. Exfoliation of the skin, pigmentation, hyperkeratoses, pemphigoid eruptions and herpes were prominent features in their cases. Reynolds [7] and Buchanan [8] have paid particular attention to the nervous phenomena exhibited by a large number of patients during the same epidemic. Polyneuritis was present in a number of them, and it was not infrequently associated with exfoliative dermatitis. Marked muscular atrophy with total paralysis of the affected muscles, especially of the limbs, was frequently observed. Absence of paralysis of the sphincters was a notable feature.

In a number of paretics treated with 0.15 gm. doses of neo-arsphenamin daily, Sicard and his associates [9] ascertained that if a single course of treatment were pursued until a man had received from 8 to 10 gm. and a woman from 6 to 8 gm. bilateral abolition of the Achilles reflex was the rule. The knee jerks were rarely affected. Disappearance of the Achilles reflex was not accompanied by such signs of polyneuritis as difficulty in walking, pain in the limbs or muscular atrophy. This symptom was regarded by Sicard as an important premonitory sign for extreme caution in giving further treatment. He noted that this reflex does not tend to return, at least it has not done so in several patients whom he carefully observed for more than a year. This point is also of importance since in such a case an erroneous diagnosis of tabes dorsalis might readily be made. Patients treated by Sicard with daily doses of from 0.15 to 0.3 gm. of neo-arsphenamin showed tolerance for the drug for some time. As a rule, they did not display evidences of toxemia until toward the end of the second month of treatment, by which time the total dosage would be from 11 to 12 gm. The symptoms observed were principally referable to the skin and its appendages. They consisted of pruritis, erythema, puffiness about the face, trophic nail lesions, loss of hair, plantar kerato-

6. Brooke, H. G., and Roberts, L.: The Action of Arsenic on the Skin as Observed in the Recent Epidemic of Arsenical Beer Poisoning, Brit. J. Dermat. **13**:121, 1901.

7. Reynolds: An Account of the Epidemic Outbreak of Arsenical Poisoning Occurring to Beer Drinkers in the North of England and Midland Counties in 1900, Lancet **1**:166 (Jan. 19) 1901.

8. Buchanan: Cases of Arsenical Peripheral Neuritis, Lancet **1**:170, 1901.

9. Sicard; Haguenau and Kudelski: Traitement de la syphilis nerveuse chronique. Les elements de controle de la medication novarsenicale, Bull. et mém. Soc. méd. d. hôp. de Par. **35**:833, 1919. Sicard: Traitement des contractures et des etats spasmodiques par les novarsenicaux, pseudo tabes novarsenical, ibid., p. 930.

derma, abscesses and ulcerations. All of the patients recovered except one, who succumbed to hemorrhages as a result of pharyngeal and postlingual ulcerations. Sicard and Roger [10] also treated a number of paretics with large doses of neo-arsphenamin, giving 1.8 gm. every five days until a total of 10.8 gm. had been reached. All went well until after the sixth, or last, injection when a generalized erythema appeared. Icterus soon became evident, accompanied by gastro-intestinal disturbance and the patients usually sank into a semicomatose state. The urine, normal until then, showed albumin and casts. The other symptoms soon cleared up as a rule, but those affecting the skin and its appendages followed a protracted course resulting in a generalized exfoliation and pigmentation of the body surface. All the hair fell out and the finger and toe nails were cast off. In some instances it required six months for patients to fully recover from the effects of such a course of treatment.

Sicard and Roger have mentioned a sign of impending arsenical intoxication which is provoked by applying tincture of iodin to the skin of one who is receiving arsphenamin or neo-arsphenamin. If the patient is on the verge of intoxication, they assert that this will speedily produce a vesicular dermatitis at the site of application.

Solomin [11] has reported the occurrence of arsenical polyneuritis in a woman who had received three injections of arsphenamin, 0.3 gm. each, within a week's time. One month later she noticed weakness in both legs associated with hyperesthesia and paresthesia. These symptoms were soon followed by paralysis and muscular atrophy of both lower legs, the extensors being most markedly affected. She recovered after three months.

The case observed by Variot and Bouquier [12] shows the cumulative effect of arsenic in a 13-year-old child who had received three series of injections of arsphenamin, or twenty-one in all. The initial dose in each series was 0.15 gm. and the last one 0.45 gm. An injection had been given every eight days with three weeks repose between series. May 16, 1918, was the date of the last treatment. Early in that same month the patient had complained of pain in the left leg associated with formication. At that time the left foot could be lifted with difficulty. Two weeks later, when first seen by Variot and Bouquier,

10. Sicard and Roger: Arsénothérapie intraveineuse intensive et l'abolition du réflexe Achilléen, Bull. et mém. Soc. méd. d. hôp. de Par. **42**:585, 1918. Sicard and Roger: Intoxication arsénicale chronique après arsénobenzothérapie intraveineuse intensive, ibid., p. 181.

11. Solomin: More on the Therapeutic Action of 606 and That of 914; Cases of Polyneuritis After the Application of Them Both, Med. Obozr. **79**:587, 1913.

12. Variot and Bouquier: Polynévrite consécutive à un traitement par l'arsénobenzol, Bull. et mém. Soc. méd. d. hôp. de Par. **42**:783, 1918.

the right foot and leg were similarly affected and a steppage gait was present. Muscular atrophy of the calf muscles appeared soon afterward. There was no disturbance of sensation. The Achilles reflexes and knee jerks were abolished. The reporters of the case did not discover evidences of any other factor capable of provoking these symptoms and they ascribed them to arsphenamin.

Abadie, Petges and Desqueyroux,[13] as well as Astié,[14] have fully described a case of polyneuritis following a 0.60 gm. dose of arsphenamin. Severe lancinating pains first appeared in the calves and thighs. Later complete paralysis of both arms and legs was noted. The face, trunk and sphincters were not affected. Marked muscular atrophy appeared later. The patient made a slow recovery without further treatment.

Pürkhauer and Mauss[15] have noted the association of Korsakow's psychosis with polyneuritis in a female tabetic who had received two injections of neo-arsphenamin, 0.45 gm. each, one week apart. Two days after the last treatment the patient, who up to this time had apparently been in good physical and mental condition, showed a loss of muscular power in both legs. Her gait became uncertain like that of a drunken person. The affected muscles were painful on pressure. About this time the symptoms of psychosis polyneuritica appeared. She grew steadily worse and died ten days after the last injection.

Bayet[16] has reported a case of multiple neuritis involving both hands and forearms followed by atrophy of the interossei of the thumbs. The patient, a young woman, presenting a macular exanthem had received five injections of neo-arsphenamin, a total dosage of 2.5 gm. within two weeks.

An interesting case of polyneuritis following acute arsenic poisoning has been reported by Raymond and Lejonne.[17] The patient had accidently taken 5 gm. of rat poison containing arsenous acid. Symptoms of polyneuritis appeared three weeks later and involved all of the extremities. The nerve trunks were painful on pressure; the

13. Abadie; Petges and Desqueyroux: Polynévrite sensitivo-motrice avec troubles psychiques à la suite d'une injection intraveineuse de salvarsan, Ann. de derm. et syph. **4**:17, 1913.

14. Astié: Les complications nerveuses dans le cours du traitement de la syphilis par le 606, Thèse de Bordeaux, 1912.

15. Pürkhauer and Mauss: Ein Fall von Polyneuritis mit Korsakowscher Psychose nach Neosalvarsan mit letalem Ausgang, München. med. Wchnschr. **61**:423, 1914.

16. Bayet: Le néosalvarsan, Presse méd. Belge **64**:755, 1912.

17. Raymond et Lejonne: Polynévrite consécutive à un empoisonment par l'arsénic, Rev. neurol. **14**:79, 1906.

Achilles reflexes were abolished; knee jerks were diminished. Paralysis of the affected parts and later a marked muscular atrophy were salient features.

CASES OF PERIPHERAL NERVE INVOLVEMENT DUE TO SYPHILIS AND MERCURY REPORTED IN THE LITERATURE

Having referred to cases of arsenical polyneuritis, let us discuss briefly instances of peripheral nerve involvement due to syphilis and also mercury.

Most of the cases of true syphilitic polyneuritis, as reported by Fordyce,[18] Fournier,[19] Cestan,[20] Spillmann and Etienne,[21] Raymond, Grosz,[22] Plehn,[23] Gilles de la Tourette, Middleton,[24] Leyden, Trömner,[25] Demanche and Menard,[26] Steinert,[27] and Nonne appeared early in the secondary period, were associated with active lesions of syphilis and responded to specific treatment.

Fordyce's case, which seems to be unique in American literature, may well serve as an example. A man aged 40, presented a macular exanthem and characteristic adenopathy. His chief complaint was inability to walk. The muscles below the knees were tender on deep pressure. Knee jerks were absent. Later distinct atrophy of the leg muscles appeared, affecting especially those below the knees. The bladder and rectum functioned normally. Mercurial treatment effected a quick recovery. Nolda[28] has reported a case of polyneuritis associated with mucous patches of the uvula, soft palate and right tonsil. The nerve trunks of both arms and legs were painful on pressure. Sensation was not disturbed. The symptoms became much worse after a prolonged alcoholic bout and resulted in a complete paralysis of

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18. Fordyce: Peripheral Neuritis of Syphilitic Origin, J. Cutan. & Gen.-Urin. Dis. **9**:174, 1891.

19. Fournier: Traité de la syphilis, Paris, J. Rueff, Editor **1**:663, 1906.

20. Cestan: Polynévrite syphilitique, Nouv. Iconog. de le Salpétrière **13**: 153, 1900.

21. Spillmann and Etienne: Polynévrite diffuse dans la periode secondaire de la syphilis, Ann. de derm. et syph. **27**:637, 1906.

22. Grosz: Neuritis Multiplex in Secunärstadium der Syphilis, Wien. klin. Wchnschr. **10**:572, 1897.

23. Plehn: Berl. klin. Wchnschr. **42**:1019, 1905.

24. Middleton: Glasgow M. J. **45**:56, 1896.

25. Trömner: Nervensyphilis der Frühperiode, Dermatologische Studien. Festschr. f. P. G. Unna **21**:339, 1910.

26. Demanche et Menard: La polynévrite syphilitique existe-t-elle? Presse méd. **19**:931, 1911.

27. Steinert: Ueber Polyneuritis Syphilitica, München. med. Wchnschr. **56**: 1938 and 2010, 1909.

28. Nolda: Neurotabes Alcoholica, oder Syphilitica oder Mercurialis. Neurol. Centralbl. **14**:200, 1895.

both lower legs. Up to that time the patient had refused mercurial trteatment for fear of being poisoned. A course of mercuric chlorid injections brought about a marked improvement, but there was a relapse after another spree. An example of polyneuritis affecting all four extremities appearing simultaneously with tertiary skin lesions has been observed by Bonnet and Laurent.[29] A primary lesion had been present five years before. Mercury cleared up the lesions in a short time.

The existence of a true mercurial polyneuritis has been much disputed, but nevertheless such cases, though rare, have occurred. Leyden,[30] Spillmann and Etienne,[31] Ketli, Faworski,[32] Brauer,[33] and Petren [34] have made contributions to this subject. The most typical cases, those of Ketli and Faworski, resulted from acute intoxication and did not occur during the course of treatment for syphilis. Ketli's patient swallowed 2 ounces of a 1 per cent. solution of corrosive sublimate, from the first effects of which he apparently recovered. Later symptoms of polyneuritis appeared successively in the feet, legs, hands and arms. Death resulted from asphyxia. In Faworski's case 20 grains of mercuric chlorid were accidently swallowed. Ten days later, after the first effects of the drug had passed away, there was total paralysis of the legs and arms. The extensor muscles were most severely affected, and the nerve trunks were painful on pressure. Recovery ensued, but very slowly. The three patients studied by Spillmann and Etienne presented in addition to multiple neuritis, well marked stomatitis and diarrhea. Two of them were undergoing treatment for syphilis. One of the latter patients had taken 160 yellow mercuric iodid pills each containing ¼ grain of that preparation and had moreover received eleven mercurial inunctions, all within twenty days. The other one, a patient in poor condition, had received six weekly injections of mercury thymol acetate, following which he developed a severe stomatitis and diarrhea and later multiple neuritis of the legs and arms. Severe albuminuria and the presence of mercury in the urine were features in both cases. The patients recovered when the

29. Bonnet and Laurent: Polynévrite syphilitique, Ann. de derm. et syph. **1**:433, 1910.

30. Leyden: Ueber Polyneuritis Mercurialis, Deutsch. med. Wchnschr. **19**: 733, 1893.

31. Spillmann and Etienne: Polynévrites dans l'intoxication hydrargyrique aigue et subaigue, Rev. de méd. **15**:1009, 1895.

32. Faworski: Zur Lehre von der acuten Merkuriellen Polyneuritis, Neurol. Centralbl. **19**:377, 1900.

33. Brauer: Letal endende Polyneuritis bei einem mit Quecksilber behandelten Syphilitischen, Berl. klin. Wchnschr. **13**:14, 1897.

34. Petren: Sur la question de la polynévrite syphilitique ou mercurielle, observation d'un cas mortel, Nouv. iconog. de la Salpétrière **28**:226, 1916-1917.

mercury treatments were stopped. The third patient showed no signs of syphilis, but had been treated by a druggist for an acute gonorrheal urethritis and epididymitis. He had been given a mixture for internal use which was found to contain a considerable amount of mercury. Mercurial ointment had been freely applied to the affected testicle for several months and the medicine had been faithfully taken for a like period before untoward symptoms appeared. Petren's case occurred in a syphilitic patient who had received several courses of insoluble mercurial injections. He later showed evidences of polyneuritis and succumbed to what that writer called mercurial poisoning. The necropsy did not help to clear up the etiology.

REPORT OF A CASE

History.—E. P., a negro, aged 42, was admitted to the Sceleth Hospital, House of Correction, on March 19, 1919. He complained of feeling weak and chilly, but walked in unassisted from the cell house. He denied ever having had syphilis, but admitted having been a heavy whisky drinker for twenty years. Soon after becoming an inmate of the institution his Wassermann reaction had been reported as ++. A careful examination made at that time had failed to reveal any other evidence of syphilis, either hereditary or acquired. Soon thereafter antisyphilitic treatment was begun and carried out as follows: The first course consisted of six weekly intravenous injections of neo-arsphenamin (neodiarsenol brand) given in concentrated solution, as Duhot and Ravaut were the first to suggest. The initial dose was 0.60 gm., subsequently he received 0.90 gm. Besides this, a dozen intramuscular injections of mercuric chlorid (1 per cent. solution) were given. No evidences of intolerance appeared during this time.

After three weeks' rest a second course was begun, since the patient's Wassermann reaction was still positive. He had received two more weekly injections of neo-arsphenamin, 0.90 gm. each, when he suddenly became ill and was admitted to the hospital the day following his last treatment.

Examination.—When admitted his temperature was 99 F., pulse 90 and respiration 20 per minute. A careful examination showed the heart, lungs, abdominal viscera and extremities to be negative. The reflexes were normal. There were no Babinski reflex, tremor or ataxia. The pupils reacted to light and accommodation. A moderate degree of pharyngitis was present.

The patient was a well built man, 6 feet tall and weighed about 175 pounds. He was first seen by the author, March 21. At that time he presented a marked, more or less generalized eruption not unlike a papular urticaria. It was most prominent over the face and anterior surface of the trunk. The lesions were pinhead sized, moderately firm papules which showed no tendency to grouping They were intensely pruritic. The next day his face was greatly swollen, the eyes being almost closed. The skin felt firm and infiltrated and showed evidence of slight scaling, especially about the face, where the papular lesions were less prominent than on the day before. Four days later the entire skin surface was the seat of an extensive exfoliation. At first the scales were small, dry and of a grayish color. Later they were much larger, especially over the hands and feet, finger cot like casts of several fingers and

toes being shed. The edema had become more or less generalized, being very evident over the scalp. The skin condition was diagnosed as exfoliative dermatitis at that time.

A blood examination made on March 25 showed the erythrocytes to be almost normal in number, the leukocytes 21,600 per cubic millimeter and hemoglobin 90 per cent. A urinalysis showed the presence of bile pigment as well as a few hyaline and granular casts. Albumin and sugar were not found then or later.

Course and Treatment.—About April 1 a bilateral mucopurulent conjunctivitis appeared and remained for several weeks. The edema was much lessened. The patient by this time was commencing to show emaciation. As a result of industrious scratching, numerous excoriations and foci of superficial infection were present especially over the lower back, flanks, thighs, shoulders and abdomen. Early in that same month bed sores appeared in the sacral region and about both heels. These ultimately became extensive and reached down to the underlying bony structures. The sacral sore attained a diameter of almost 10 cm. During a large part of April the patient was irrational. Dr. Sidney Kuh saw him late in that month and stated that any mental disturbance present was probably of toxemic origin.

Early in May a large abscess appeared below the angle of the left scapula. The exfoliation, though still present, was appreciably diminished. About this time the patient said that he felt sharp pains in his feet and in the lower part of his legs. A little later he exhibited a slight steppage gait. His hands also began to show signs of weakness and it was difficult for him to grasp and retain objects. On May 11, foot and wrist drop appeared, the former being more marked. Beginning in the toes and the fingers, this condition gradually extended upward to the lower part of the legs and to the forearms, although they were affected to a lesser degree than the more distal parts. By this time he could not stand or raise himself up and had to be fed. The Achilles reflexes were almost abolished, but the knee jerks showed only a slight diminution. The affected muscles were tender on pressure. Muscular atrophy appeared soon after the paralysis, coming first in the feet and hands and thence extending centripetally in a like manner. There was no interference with either the rectum or bladder.

Dr. Kuh was kind enough to examine the case again, June 19, with the following result: "Complete paralysis of all muscles below the knees with marked atrophy; paresis and somewhat less marked atrophy of leg muscles above the knees; contractures of both calf and hamstring muscles; tendo Achilles reflex very slight. Knee jerks fairly brisk; adductor reflex present; no impairment of sensation in extremities; loss of muscular grip more marked on left side than on right; some contractures of flexors of upper arms and diffuse paresis of all the muscles of upper extremities; no disturbances of the cranial nerves; pectoralis major and deltoid muscles good."

From these findings the case was regarded as one of polyneuritis. A flaccid paralysis beginning peripherally and extending centripetally, accompanied by muscular atrophy, prodromal pains in the extremities, marked pain in affected parts on pressure, absence of bladder or rectal disturbance, absence of Babinski's sign and lack of pupillary changes would speak in favor of such a diagnosis. Pierre Marie[35] and others contend that such cases are almost

35. Marie, Pierre: Les polynévrites, Rev. gén. de clin. et de thérap. **32**: 116, 1918.

always accompanied by slight cord and even brain changes, but of course the most marked changes are present in the peripheral nerves.

A fatal termination was looked for on at least three occasions. Symptoms of a marked toxemia such as a high fever were present for almost three months. The fever reached its acme 104 F. on April 2. Then came a short remission and then another siege of fever lasting about two weeks. At that time 103.8 F. was the highest point reached. On April 2, perhaps the most critical day, the pulse was 144 and the respiration 36 per minute There was no fever after July 1. The patient lost all of his hair as well as his nails. Diarrhea was present for a time early in April, but not after the nervous symptoms appeared.

In spite of such a serious illness he has apparently made a perfect recovery. When discharged from the hospital, August 7, 1919, he was thin and weak. When seen about two months later he had gained considerably, although he still exhibited a steppage gait, which has now disappeared. At the present time he has so far recovered as to be able to perform nightly as a cabaret entertainer.

The treatment employed was directed toward supporting his strength, cleansing the skin surface and causing the bed sores to heal. Internally, he received for some time quinin sulphate, as Engman and Mook have suggested in cases of exfoliative dermatitis. Later this was replaced by elixir of iron, quinin and strychnin. Locally, a dusting powder of zinc oxid and talcum was employed. Later when the skin was more or less generally infected prolonged baths in a warm dilute solution of potassium permanganate were of distinct value. The bed sores healed slowly under long daily exposures to sunlight and air.

ETIOLOGY OF CASE

There appears to be no reason to doubt that neo-arsphenamin by virtue of its arsenic content was the chief factor in the case. The symptoms were like those following arsenical intoxication. As Obermiller [36] has said in speaking of paralysis due to these arsenical compounds, when grave toxic symptoms appear only after repeated injections one must think of a cumulative effect of the agent employed. Here the drug acted on one already more or less poisoned by alcohol and syphilis, making it easy for the arsenic to assert its well-known affinity for nervous tissue.

Against syphilis being the determining factor is the fact that cases of multiple neuritis due to that disease are, as has already been stated, almost always observed during the secondary period in association with active skin manifestations. The fact that the patient recovered without further specific treatment would also speak against syphilis. Both syphilis and alcohol, however, were doubtless contributory causes.

It would seem altogether unlikely that the symptoms observed in this patient were the result of mercurial intoxication. If so extensive a condition were due to mercury, we should expect to find stomatitis, more marked evidences of gastro-intestinal disturbances, and probably

36. Obermiller: Ueber Arsenlähmungen, Berl. klin Wchnschr. **50**:966, 1913.

nephritis with a large amount of albumin in the urine. Another point against mercurial poisoning is that most cases of intoxication after injections of mercury follow the use of the insoluble salts, such as calomel and gray oil, and few are noted after mercuric chlorid, as a perusal of Lasserre's [37] exhaustive paper and Levy Bing's [38] thesis will show.

In closing, I wish to express my thanks to Charles E. Sceleth, Dr. Sidney Kuh and other members of the staff of the House of Correction for aid in the study of this case.

32 North State Street.

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37. Lasserre: Le passif des injections mercurielles, Ann. de derm. et syph. 9:215, 289, 655, 707, 1908.

38 Bing, Levy: Les injections mercurielles intramusculaires dans le traitement de la syphilis, Thése de Par., 1902.

THE PROVOCATIVE PROCEDURES IN THE DIAGNOSIS OF SYPHILIS *

PAUL A. O'LEARY, M.D.
Section on Dermatology and Syphilology, Mayo Clinic
ROCHESTER, MINN.

In June, 1917, Dr. J. H. Stokes and I [1] undertook the study of the effect of a small dose of arsphenamin in provoking a positive Wassermann reaction in previously negative blood serum in 103 cases, paying special attention to the value of the test in the diagnosis of obscure syphilis. I propose to review the results of a second series of 285 cases and of a special group of thirty Wassermann series. The provocation of the Wassermann reaction following an injection of arsphenamin was first suggested by Gennerich [2] in 1910; it was confirmed by Milian,[3] and later advocated as a useful procedure by other syphilographers of note in this country. Craig [4] believes that a normal variation occurs in successive Wassermann tests of the same patient. He does not believe that the fluctuation is due to technical error. Haller,[5] however, in a similar review attributed such fluctuations to technical difficulties and not to any variation in the complement-binding power of the serums.

From our previous review we estimated that apparent provocation of the serum Wassermann reaction occurred in 18 per cent. of the patients subjected to a provocative injection of arsphenamin. We obtained presumptive, though not conclusive, evidence that such a phenomenon as a provocative reaction exists. It seemed probable that variations in the technic and reagents are factors in the result. With reference to its diagnostic worth, we believed that in cases in which the test was most needed it offered the least help. In other words, we found the highest percentage of reversals in the cases showing the

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* Read before the Section on Dermatology at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

1. Stokes, J. H., and O'Leary, P. A.: The Provocative Wassermann Test in the Clinical Diagnosis of Syphilis, Am. J. Syphilis **1**:629, 1917.

2. Gennerich: Ueber Syphilisbehandlung mit Ehrlich 606, Berl. klin. Wchnschr. **47**:1735, 1910.

3. Milian, Quoted in Craig, C. F.: The Results and Interpretation of the Wassermann Test, Am. J. M. Sc. **149**: 1915.

4. Craig, C. F.: The Results and Interpretation of the Wassermann Test, Am. J. M. Sc. **149**:41, 1915. The Wassermann Test, St. Louis, Mosby, 1918, Chap. III.

5. Haller, D. A.: Variations in the Strength of Positive Wassermann Reactions in Cases of Untreated Syphilis, J. A. M. A. **66**:882, 1916.

most clinical evidence of syphilis. In view of this relation, we were forced to conclude that the test was inferior both to clinical judgment and to the therapeutic test in the recognition of obscure syphilis.

Our second provocative procedure in contrast with our first was based on a conservative Wassermann test made with one Noguchi antigen,[6] and is probably, therefore, relatively free from the deceptive effects which may be obtained by overcholesterinized antigens. Even with the employment of sensitive antigens in our first series we were compelled to conclude that the provocative test has a value in diagnosis of less than one-third that of the therapeutic test and of clinical judgment. The employment of a conservative technic in the second series, as will be seen, still further reduced its relative value.

The indications for a provocative test as determined by the previous work are not discussed separately, because they have proved to be practically identical with the indication for expert syphilologic examination in general. Suffice it to say, that we believe what we call the provocative test is still a necessary procedure in a complete and thorough examination for syphilis whether the suspicion is aroused by clinical evidence or history.

COMPARISON OF RESULTS OF FIRST AND SECOND SERIES OF TESTS

The ideal provocative Wassermann test, conducted so as to provide for every possibility, is not worth the necessary time, labor or expense. As a practical compromise, the blood of each patient, including the blood drawn just before the intravenous injection of arsphenamin was given, was examined daily for seven days.

At the request of the Section on Dermatology and Syphilology, patients who were undergoing the provocative test were meanwhile subjected to special examinations in various departments of the Clinic for evidence of syphilis. An examination of the spinal fluid was made almost as a routine procedure in this particular series. In the 285 cases studied provocation of the serum Wassermann reaction was obtained in 8 per cent. (twenty-three patients) as contrasted with 18.4 per cent. in the first series. We attribute this discrepancy to the difference between the very sensitive Wassermann technic of the first series,

6. The Wassermann technic as done at the clinic under the direction of Dr. A. H. Sanford is a slight modification of the original Noguchi system. In the preparation of the amboceptor, dogs have been used instead of rabbits. Human corpuscles have been sensitized by adding a definite amount of amboceptor to the washed corpuscles and placing the mixture over night in the ice box. The sensitized cells are then titrated against various amounts of 40 per cent. diluted guinea-pig serum. The standard antigen for routine work is an acetone-insoluble fraction of heart extracts.

including multiple and cholesterinized antigens, and the conservative technic of the second series.

In the course of the series of tests, it was noted that from time to time a patient in whom a provocative effect was expected, presented a positive Wassermann reaction on the blood drawn immediately before the arsphenamin injection. Such cases are obviously not provocative effects and should be classified under the group of Wassermann series. In order to aid in determining whether or not the provocative procedure had any intrinsic value, this observation was extended by the performance of thirty series of seven Wassermann tests each on as many patients, without any provocative injection. The fact that 30 per cent. of the patients thus examined yielded positive tests in the course of the series furnishes convincing evidence that even though a provocative effect may exist as such, much of the clinical value of the so-called provocative test lies in the series of Wassermann reactions which it calls for rather than in the results of an injection of arsphenamin. A series of seven Wassermann tests appears to afford an excellent means of interpreting the fluctuations of the ordinary Wassermann technic which Craig believes are to be expected. Why the percentage of the positive results in the Wassermann series should have been higher than in the provocative it is difficult to say unless we unconsciously selected for this procedure patients who were more probably syphilitic.

In our previous report, and in fact throughout the literature, are numerous citations of graded increases and decreases of the provocative effect from day to day. In the series here reported only two examples of such gradations were observed. The taking of blood at twenty-four hour intervals is a crude means of detecting such gradations, so that I believe it quite safe to trust a complete and sudden reversal from negative to positive and back again without intermediate gradations. The second series of provocative tests has impressed on us the fact that it is impossible to predict the day on which a provocative or a Wassermann series will reverse from negative to positive. Accordingly, all systems in which blood is drawn on specified days after the injection appeal to us as untrustworthy. We may say, however, that no provocative reversal was secured after the eighth day and the majority of the changes from negative to positive occurred between the second and fifth days, inclusive (60 per cent.). Repeated examples were seen in which subsequent clinical and serologic findings confirmed the significance of a single positive test among six negatives.

In our previous report, the belief was expressed that the provocative effect and the Herxheimer reaction to which it has been compared are not necessarily identical. In the second series I had occasion to note the presence of a positive local Herxheimer reaction in the absence

of provocative action on the serum in six cases. This fact I believe entitles the Herxheimer reaction to a separate, though not especially important, place among the diagnostic elements of a provocative procedure and makes it imperative that any patient sustaining a provocative series in the presence of an obvious lesion should be observed daily for signs of local reaction.

The vogue of the provocative as a test for cure has declined decidedly of late owing in part to Pollitzer and Spiegel's [7] effective criticism. In our first provocative series we emphasized this feature in the use of the test and were of the opinion that it was of some assistance in reactivating negative Wassermann reactions. In the second series, forty-three patients were examined for the fact of cure. All of them gave definite histories of desultory treatment and presented no clinical signs of the disease. A positive provocative effect was secured in six cases. While these positive effects are valuable and should be tested for, our results fully confirm Pollitzer and Spiegel's observations that positive Wassermann reactions can be secured months after a completely negative provocative test. We found, further, that in the presence of a completely negative provocative test on the blood we were able to obtain positive evidence of syphilis in the spinal fluid in eight cases.

A negative provocative test by no means excludes syphilis from the diagnosis. We were able to show in our first series and to confirm in the present series that 35 per cent. of the patients from whom negative results were obtained are demonstrably syphilitic on therapeutic test. A provocative procedure can, therefore, never be regarded as a last resort and must be continued to a more nearly complete therapeutic test if clinical judgment, based on the history and special examination, seems to warrant it. Emphasis should be placed on the fact that a single arsphenamin injection in superficial lesions has a decided value as a therapeutic test and that this value properly attaches to the provocative procedure as a diagnostic aid.

CONCLUSIONS

Four years of observation of the provocative procedure have convinced us that the same fundamental principles underlie the interpretation of the Wassermann part of the test which underlie the clinical interpretation of the Wassermann test in every phase of the diagnosis of syphilis. The estimation of the sensitiveness or conservatism of the test, acquaintance with the antigens used, and a knowledge of the temperamental tendency of the serologist and of the methods employed

7. Pollitzer, S., and Spiegel, L.: The "Provocative" Wassermann Test, Am. J. Syphilis **3**:252, 1919.

in his laboratories are absolutely essential. I have little doubt that with a hypersensitive technic a series of seven Wassermann tests, with or without a preliminary arsphenamin injection, could become a dangerous instrument for the production of false clinical diagnoses. On the other hand, in a technic of average sensitiveness there is little doubt that the test adds from 10 to 20 per cent. to the acuteness of the ordinary Wassermann test, and does so without a correspondingly increased risk of false positives, as with highly cholesterinized antigens. Our second series of provocative tests has convinced us as firmly as the first that clinical judgment and the intensive therapeutic test have an efficiency as diagnostic aids which is two or three times as great as the provocative procedure per se.

SUMMARY

1. The provocative procedure employed by the Section of Dermatology and Syphilology of the Mayo Clinic consists of a single intravenous injection of 3 decigrams of arsphenamin, with a series of seven Wassermann tests made at twenty-four-hour intervals, the first blood being drawn just before the arsphenamin injection, and if indicated, daily observation of the patient.

2. Four factors contribute to the diagnostic worth of the procedure: (a) A true provocative effect on the Wassermann reaction. (b) The advantage of a series of Wassermann tests which strikes the average and assists in the interpretation of the spontaneous or technical variations of the ordinary Wassermann test. (c) An opportunity to observe a focal flare-up in a visible lesion, the "Jarisch-Herxheimer reaction." (d) The beginning of the therapeutic test. About one fourth of the value of the procedure is ascribed to the provocative effect, one-half to the Wassermann series, and the remaining fourth is divided between the Herzheimer reaction and the therapeutic response elicited. The provocative procedure, including the Wassermann series, Herzheimer reaction, and early therapeutic effect, adds about 16 per cent. to the sensitiveness of a conservative Wassermann test in the diagnosis of syphilis.

3. Although I believe that gradations in the strength of the true provocative effect are not essential to a positive result, and although a single positive reaction among a number of negative reactions is usually significant, it must be remembered that the provocative procedure here described is subject to the same margin of error and calls for the same interpretation of serologic methods as the Wassermann reaction itself. False positive tests and persistent negative results in the presence of syphilis may occur as in all Wassermann test technics.

4. The use of hypersensitive antigens in a provocative procedure is to be deprecated, since they increase the risk of false positive results beyond the point justified by the general value of the procedure in diagnosis.

5. A negative provocative test does not establish the fact of cure, but a positive provocative result is of assistance in recognizing an infection which might otherwise have remained concealed.

6. The provocative procedure described is of no value alone, and should be regarded merely as a part of a general syphilologic examination. The procedure, for example, may yield negative results in the presence of positive spinal fluid findings.

7. The provocative procedure is not a substitute for clinical judgment, and should be regarded in doubtful cases merely as the beginning of a therapeutic test.

I wish to acknowledge the assistance of my chief, Dr. John H. Stokes, in the arrangement of this material.

STABILITY OF SILVER STAINS AS APPLIED TO SPIRILLAR ORGANISMS

TOMÁS G. PERRÍN, M.D.
Professor Emeritus of the University of Michoacán
MEXICO, D. F.

The silver stains for smears, so frequently applied in the examination of treponemes and leptospiras, and now practically limited to the method of Fontana-Tribondeau and Holland's modification, present a serious disadvantage on account of their inevitable discoloration, more or less rapid, through the action of physical agents (long exposure to the light) or chemical agents (action of the cedar oil used in the immersion).

In view of the beauty of these methods, their importance in microbioscopic preparations for teaching purposes and their unsurpassed advantages in photomicrography, I shall describe the simple technic with which we have succeeded in stabilizing these dyes.

The method consists simply in submitting the stain to the action of a fixing and toning bath. The solution may be placed on the surface of the slide or the latter, already treated by the method of Fontana-Tribondeau, may be tipped into Borrel bottle filled with the solution. As happens in the case of photographic positives, an intensification of color follows a slight discoloration of the silvered surface, finally acquiring a permanent depth. The slide is then taken out, washed and left to dry.

The foregoing chemical changes no longer permit us to consider the preparation a silver dye. The sodium hyposulphite of the fixative having reacted on the silver chlorid (this is formed through interaction of the chlorin from aurous chlorid and silver nitrate), a double hyposulphite of gold and sodium results which gives the ultimate color to the parasites. If lead salts have been employed instead of gold chlorid, as occurs in the majority of fixing and toning baths, pentathionic acid gives the ultimate tone.

The practical result is that the preparations show the microbes stained dark gray—when the lead salts are emp'oyed—or bluish black —with the gold salts—both being stable. In addition, the yellow background of the preparation disappears entirely through the transformation of the silver nitrate into silver chlorid and dissolution of the latter in the hyposulphite.

Photomicrograph 1 was obtained with a preparation of treponemes which had been exposed for two months to daylight. In the control

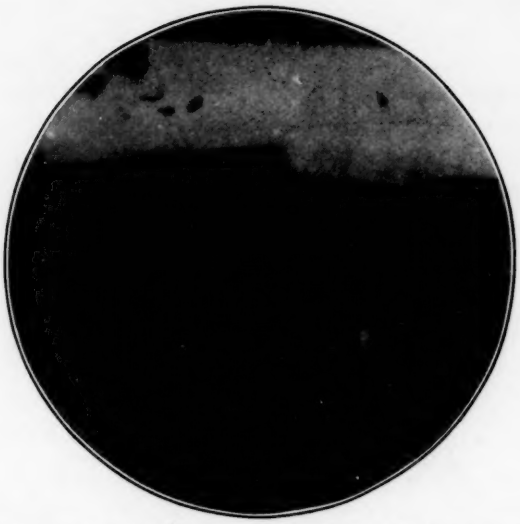

Fig. 1.—Treponeme preparation exposed to daylight for two months after stabilizing.

Fig. 2.—*Leptospira icteroides* preparation stabilized two months after being prepared.

preparation, not stabilized according to our method and undergoing the same light action, the treponemas were indistinguishable after three weeks.

Photomicrograph 2 shows a preparation of *Leptospira icteroides* made by Dr. Hideyo Noguchi, Jan. 4, 1920. Two months later the leptospiras could be detected with difficulty. After treating with our technic in a gold fixing bath, we secured a much better staining of the parasites, in addition to a stable color.

The best results are, of course, obtained in preparations stained recently with silver.

As we have indicated, the commercial fixing baths gave good results (the one we employed for the treponemes was manufactured

Fig. 3.—Spirillar organisms of Riggs' disease after being stabilized.

by Burke & James, Chicago). If a black coloring is desired—which may be obtained exclusively through the action of gold and is very stable—one can employ, after fixing in hyposulphite, a toning bath much valued by photographers. This was described by Professor Namias in 1910 before the International Congress of Photography in Brussels, and is of the following composition:

	Gm.
Sulphocyanid of ammonium	6.25
Tartaric acid (or citric acid)	0.50
Sodium chlorid	1.25
Water	250.00
Solution of gold chlorid, 1:100	6.25

This formula was employed to stabilize the preparation shown in Photomicrograph 3 (spirillar organisms of Riggs' disease).

Apart from the evident usefulness of this practice of fixing, this technic might suggest other experiments in photographic chemistry, especially in the utilization of platinum, a metal which, as is known, resists powerfully the action of physical and chemical agents. It would also be interesting to apply it to preparations of parasites in the tissues treated with Levaditi-Manouelian's technic, or the most recent one of Warthin and Starry.

A CASE OF LICHEN PLANUS LINEARIS: ITS RELATION TO A CUTANEOUS NERVE EXPERIMENTALLY SHOWN *

LLOYD W. KETRON, M.D.

BALTIMORE

Lichen planus occurring in narrow lines, although comparatively rare, has been recognized for a number of years. The condition was known to Cazenave and Devergie as "lichen en ruban" as early as 1843. In most of the cases, since reported, the eruption has apparently followed the course of a cutaneous nerve, especially the small sciatic. Examples of this distribution have been presented to the London Dermatological Society by Crocker, Morris, Pringle and Galloway.

A few cases, however, have been reported in which the eruption followed the courses of other nerves. In one of Mackenzie's cases it followed that of the left ulnar and internal cutaneous nerves and in another it began in the course of some of the intercostal nerves, subsequently becoming general.

More rarely the linear eruption has not apparently followed a nerve, as in Meyer's case in which it was supposed to have followed Voight's lines and in Perry's case in which it corresponded to the course of the long sapheneous vein.[1]

REPORT OF CASE

History.—A carpenter, aged 33, came to the Johns Hopkins Hospital Dispensary in January, 1915. He had had no serious illness and usually enjoyed moderately good health. He did not appear to be of a nervous or excitable nature and had no worries other than those of the average workingman. There was no history of any previous skin disease.

The eruption of which he complained had been present fourteen or fifteen years. It had begun on the back of the right hand and had reached its present dimensions gradually within four or five years. It had practically remained unchanged for the past ten years. Itching was the only subjective symptom and this was not especially marked except when the patient became overheated.

Examination.—The disease was distributed as a narrow band, beginning just above the external condyle of the humerus and extending down over the extensor surface of the forearm and hand ending about the middle of the index finger. The line was practically unbroken and varied in width from 2 to 6 cm. It consisted of discrete or confluent, pinkish or dark red papules from 2 to 5 mm. in

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* Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April 22, 1920.

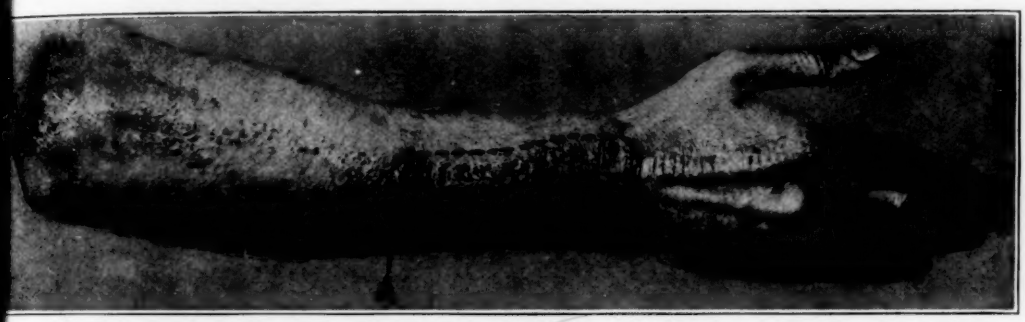
* From the Department of Dermatology, Johns Hopkins University, Medical Dept.

1. Other cases are reported by Crocker: Brit. J. Dermat. **42**:421, 1900.

diameter. Some of the lesions on the back of the hand were umbilicated and smooth, but most of these on the arm were covered with whitish scales or hemorrhagic crusts as the result of scratching.

The clinical diagnosis of lichen planus linearis was made and substantiated by the histologic examination. The eruption followed the course of the inferior external branch of the musculospiral nerve to its cutaneous end, which is usually at the wrist. Beyond this point it lay on territory supplied by one of the branches of the radial nerve.

Treatment and Course.—Because of the possibility of the disease being dependent on some disturbance in this branch of the musculospiral nerve, it was thought advisable to sever it and note the effect on the eruption. An incision was made through the skin at right angles to the affected line about the middle of its course. It was carried through the subcutaneous tissue beneath which a small nerve trunk about 2 mm. in diameter was found lying on the muscular fascia. This nerve lay directly beneath the eruption and at this point ran parallel to it. The nerve was severed and a small piece removed for histologic examination. (This piece was unfortunately lost during fixation.)



Lichen planus linearis on the arm of author's patient. A, point at which nerve was cut; dotted line encloses approximately the anesthetic area.

The effect of severing the nerve was to produce an area of complete anesthesia to pin pricks which extended 11 cm. below the point of incision and ended just above the level of the lower end of the radius. This anesthetic area followed the course of the eruption and averaged about 3 cm. in width. All of the lesions in this area lay within it. The patient was observed for two or three weeks and then lost sight of for seven months. An examination at the expiration of this time showed that there was no noticeable change in the appearance of the disease and that the area of anesthesia had completely disappeared except over the scar from the incision. He also reported that he had noticed no change in the disease during his absence except the loss of itching over the anesthetic area.

The investigation of this case proves beyond doubt that the eruption of lichen planus followed the course of a cutaneous nerve for about one third of its length, as shown by the co-existence of the anesthetic area and the eruption. It can justifiably be assumed that the remaining portion of the eruption, central to the point of incision, followed the same nerve since it follows the usual course of this nerve and lies within the territory usually supplied by its branches. The portion of

the disease over the back of the hand and finger, distal to the lower limit of anesthesia, may have followed the same nerve which has overlapped the usual territory of the radial nerve or a branch of the radial itself. In the former case, protopathic sensibility must have been fully supplied to this area by the radial nerve, or at least, to such an extent that no noticeable diminution of sensation was evident. The work of Head, Rivers and Sherren [2] has shown that there is considerable overlapping and variation of the protopathic nerve fibers and that a very small area of anesthesia, compared to its anatomic distribution, may be caused by severing a cutaneous nerve.

Nothing is known of the nature of the relation of linear lichen planus to cutaneous nerves. It is difficult to conceive that the eruption follows the nerve in the sense that the latter offers an anatomic pathway along which it may be distributed. This would necessarily involve decided sensory disturbances and, furthermore, the inflammatory process of lichen planus is situated much above the usual course of the cutaneous nerve trunks.

Whatever this relation may be it is not possible, in the state of our present knowledge, to support adequately a theoretical possibility, since we know nothing concerning the etiology of the disease itself.

DISCUSSION

Dr. Wise said he always hesitated to make a diagnosis of linear lichen planus unless he saw other lichen planus lesions on the skin or in the mouth. The possibility of nevus linearis occurring in adult life had to be considered. He asked if there was other evidence of lichen planus in this case.

Dr. Ketron, replying to Dr. Wise, stated that there was no evidence of lichen planus on any other portion of the patient's body nor was there any history of it. The histologic picture, however, was typical of lichen planus, showing the round-celled infiltration of the upper portion of the corium and the characteristic epidermal changes.

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2. Head, Rivers and Sherren: Brain **28**:99, 1905.

A BORDERLINE CASE OF NEUROTIC EXCORIATIONS *

WILLIAM ALLEN PUSEY, M.D.
CHICAGO

MacKee and Senear and I have recently called attention to a group of self-inflicted eruptions, under the title "Neurotic Excoriations." In their slight degrees they are familiar, but the more extreme forms of the condition, while their character is doubtless recognized, have not hitherto been reported in this country. The subject has been described carefully by English authors, notably by Erasmus Wilson, Tilbury Fox, and Adamson. I believe the cases are so frequent that the subject should be impressed on our minds.

The clinical pictures differ from the ordinary feigned eruptions, and the conditions differ essentially from feigned eruptions in the mental states of the patients. In a feigned eruption the patient is secretive and tries to cover up the fact that the eruption is self-produced. In neurotic excoriations the patient has a strong impulse to produce damage to the skin and, while he may not suggest the part that he plays in his injuries, he makes no attempt to conceal it when inquiry is made. His is an entirely different mental attitude from that of the malingerer.

I have recently seen a case in which the amount of destruction of the skin equaled that in many cases of typical malingering, but in this case the psychic condition was that seen in neurotic excoriations. It may perhaps be regarded as a borderline case between the two conditions.

REPORT OF A CASE

History.—Miss X., aged 26, a nurse, who acted as an attendant in a doctor's office, presented herself in December, 1919, with a chronic ulcer of the back of the left hand. There was an atrophic, ulcerating scar extending the full width of the hand, and from the wrist to within a finger's breadth of the knuckles. In the scarred area there were numerous round, crescentic, irregular superficial ulcers. These superficial ulcers were covered with red granulations in which there were numerous islets of growing epithelium. There were other small deeper ulcers, some being in the skin outside the scar, and the whole area was more or less covered with yellowish pus crusts (see figure).

In September, 1918, she burned the left hand with concentrated lye. The burn healed with the formation of a thin scar. The scar was fissured from time to time across the wrist, but the fissures readily healed with zinc oxid ointment. About five weeks before presentation a fissure appeared, but this

* Read at the Forty-Third Annual Meeting of the American Dermatological Association, Asheville, N. C., April 22-24, 1920.

did not heal on the application of the zinc oxid ointment; the scar began to ulcerate, and the ulceration spread rapidly. Dressings of zinc oxid ointment and other bland ointments, of balsam of Peru, wet dressings of salt solution, hydrogen peroxid solution and the surgical solution of chlorinated soda (Dakin's solution) had been used without avail; the ulcerations continued to spread.

There was nothing significant in the patient's history. Her general health had been good. She slept well. She was an intelligent woman, and her physician employer thought that she was not nervous or high strung, although seven years before, at a time of family difficulties, she showed some tendency to hysteria. Her pharynx and conjunctivae were anesthetic.

The configuration on the back of the hand was not that of the ordinary feigned eruption, but neither did it resemble any known dermatoses. The individual lesions were such as might be produced by local injury combined with

Neurotic excoriation on hand.

simple pus infection. It was not difficult, therefore, to arrive at the conclusion that the injury was probably self-produced. The patient, however, did not present the usual facies of the malingerer. There was not the impassive face, the dejected expression, the downcast eye of the malingering woman. She was alert, looked one in the eye and answered questions without evasion. When the opinion was given that the lesions were self-produced the doctor frankly said he could not believe it. The woman, however, readily admitted that this might be true, as she had found herself constantly picking at the hand, and could not avoid it. She was not secretive or on the defensive. If she was doing it, it was through a nervous impulse which she had not been able to resist, and she was ready to cooperate with us in meeting the situation.

Treatment and Course.—I advised the application of weak aluminum acetate solution compresses and an occlusive dressing that would prevent her from getting at the hand. Two and a half weeks later her physician employer wrote me that the hand had healed completely in about a week, but in order to prevent her from irritating the hand at night, she had had to put a muff on her other

hand, and for a while it had been necessary for a nurse to watch her at night. It was at night, during her sleep, that she did most of the damage. Her physician, to whom I said nothing about neurotic excoriations of the skin, suggested in his letter that he thought she had not been producing this injury deliberately, but through nervousness, comparing the condition very aptly to biting of the fingernails. After a week and a half of treatment she needed dressings only during sleep, and was able to go on with her nursing as usual.

DISCUSSION

DR. SCHAMBERG thought Dr. Pusey did well to emphasize the distinction between the two types of factitious dermatitis which were very different in their nature and the motive which prompted them. The feigned eruptions that had as their motive a desire for morbid sympathy or escape from some unpleasant duty, were familiar as were also the so-called neurotic excoriations in which the underlying cause is an uncontrollable and vicious habit, often acquired more or less subconsciously in an effort to aid in the cure of the lesions. He had seen a number of cases of acne in which the patients had produced indelible scars on the face. The patients freely admitted their part in the production of the lesions of the face, but said the lesions would not heal until they were opened. The two types of factitious lesions were very different in their inception. Dr. Schamberg thought that one should also differentiate between neuropathic lesions of the skin of organic origin and those considered above. He recalled a patient who had been for many years under the care of Dr. Duhring whose hand was mutilated by a gangrenous process until it looked like a claw. Pathologic studies of the nerves in the amputated member were made by Professor Spiller of the University of Pennsylvania. Degenerative changes were found which were regarded as primary, but it was impossible to exclude secondary nerve change. He believed three conditions should be considered: the feigned eruptions, the neurotic excoriations and certain neuropathic changes which were due to nerve lesions.

DR. ORMSBY stated that some years ago he had recorded the cases of thirty-four patients who had produced lesions on themselves, and he had seen a number of similar instances since that time. The question frequently arose as to whether these were self-inflicted or were of spontaneous origin. He believed the major portion were self-induced. He had seen none that were spontaneous, and he was therefore interested to hear Dr. Schamberg's report of a proved spontaneous gangrene—Dr. Corlett and a few others had described similar instances. The group of patients recorded by Drs. Pusey and MacKee, while having self-induced lesions, belonged to a different category, but that some of them may be similar was well illustrated in the case reported by Dr. Pusey. Had this patient been seen some years ago it probably would have been considered an example of feigned dermatitis. The history, together with the lesions in the light of our present knowledge, removed it from that group and properly placed it with neurotic excoriations.

DR. ENGMAN believed that the sexual element was important in these cases. Some years ago he and Dr. Schwab reported a case in which there was a decided sexual element. The young woman had, when picking her skin, a distinct sexual feeling. In the case of acne excoriation there was such a history, and it was an important fact in analyzing these cases to go into the sexual history. Sometimes, in the freudian sense, it was the basis of the trouble and these patients obtained some sexual gratification in picking the skin.

DR. HAZEN said that he had seen a pruritus of the genitals develop when patients were unhappily married and also when they had failed to be married when they expected to, and he thought most cases of pruritus vulvae would fall into the same group. He believed that psychanalysis would be valuable in these cases, if it were possible to get a good man to cooperate.

DR. PUSEY (closing) said that he was familiar with the sexual element that complicated many cases of feigned eruption, but he was not inclined to think that this was an element that was apt to be encountered in neurotic excoriation. The impelling fact in these cases was the nervous impulse to pick at a lesion, and he was anti-freudian enough to believe that this impulse could reasonably be thought in most cases not to have a sexual element. He was particularly interested in the sharp mental distinction between the patient in the case he had just reported and the malingerers. He tried to bring out the contrast in the report. He had never seen a malingerer whose attitude had been the frank one of this patient.

PROTEIN SENSITIZATION IN ECZEMA

REPORT OF SEVENTY-EIGHT CASES

MAXIMILIAN A. RAMIREZ, M.D.
Associate Attending Physician to the French Hospital; Assistant Attending Physician to the City Hospital
NEW YORK

In reporting this series of cases, I especially wish to call attention to a particular phase of the clinical applicability of protein sensitization which is commanding wide interest and gaining rapidly in importance. Our present knowledge of the etiology and specific treatment of eczema is so vague, that any procedure indicating a clearer understanding of this condition is indeed worthy of special note.

In reviewing the literature on this subject, one is impressed by the variance of opinion, and results obtained. Blackfan,[1] using both the cutaneous and the intradermal method of testing, obtained a positive reaction to proteins in twenty-two of twenty-seven patients with eczema; Strickler and Goldberg[2] obtained positive reactions in six of thirteen cases tested, but these observers used only fourteen proteins and did not consider a reaction as positive unless it persisted for forty-eight hours, thus lowering the percentage of positive cases; White,[3] using proteins, butter, lactose, etc., concludes that 80 per cent. of the cases of chronic eczema are due to food sensitization. During the past few years numerous reports on the relation of anaphylaxis to eczema have appeared in the literature, but there seems to be no uniformity; I believe this is in great part due to differences in technic and standards of positive reaction.

In the following table I have not attempted to include the various metabolic studies which are necessary in the proper study of eczematous patients, but am merely submitting a record of protein skin tests in a series of eczema cases.

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1. Blackfan, K. D.: Cutaneous Reaction from Proteins in Eczema, Am. J. Dis. Child. **11**:441, 1916.

2. Strickler, A., and Goldberg, J. M.: Anaphylactic Food Reactions in Dermatology, J. A. M. A. **66**:249 (Jan. 22) 1916.

3. White, C. J.: Eczema, J. Cutan. Dis. **34**:57 (Feb.) 1916; Ibid., Boston M. & S. J. **178**:5 (Jan. 3) 1918; Ibid.: Two Modern Methods to Be Employed in the Treatment of Chronic Eczema, J. A. M. A. **68**:81 (Jan. 13) 1917.

Results of Protein Skin Tests

PATIENTS TESTED

	No. Cases
Males	52
Females	26
Under 1 year	2
Between 1 and 10	10
Between 10 and 20	8
Between 20 and 30	37
Between 30 and 40	14
Above 40	7
Total	78

PATIENTS GIVING A POSITIVE PROTEIN SKIN TEST

	No. Cases
Under 1	2
Between 1 and 10	8
Between 10 and 20	4
Between 20 and 30	12
Between 30 and 40	3
Over 40	1
Total	30

PATIENTS WITH ECZEMA ASSOCIATED WITH BRONCHIAL ASTHMA

	No. Cases
Under 1	2
Between 1 and 10	6
Between 10 and 20	2
Between 20 and 30	4
Between 30 and 40	0
Over 40	0
Total	14

PATIENTS WITH ECZEMA ASSOCIATED WITH HAY FEVER

	No. Cases
Under 1	0
Between 1 and 10	1
Between 10 and 20	1
Between 20 and 30	0
Between 30 and 40	0
Over 40	0
Total	2

ECZEMA ASSOCIATED WITH BOTH ASTHMA AND HAY FEVER

Occurring between the ages of 1 and 10	1

DURATION OF THE ECZEMA

	No. Cases
Less than one month	14
One to six months	45
One to two years	11
More than two years	8
Total	78

DISTRIBUTION

	No. Cases
One hand	40
Both hands	26
Both arms and feet	4
Face	6
Entire body	2
Total	78

RESULTS

	No. Cases
Cured	10
Improved	12
Not improved	8
Total	30

POSITIVE REACTION TO VARIOUS PROTEINS

	No. Cases
Milk (cow's)	4
Egg white	14
Whole wheat	2
Corn	7
Rice	4
Rye	2
Oats	3
Pork	3
Potato	4
Lettuce	3
Celery	8
Cabbage	2
Herring	1
Lobster	1
Crabs	1
Veal	2
Beef	3
Ragweed	4
Timothy	2
Total	70
Total number of cases reacting to a single protein	3
Cases showing multiple sensitization	27
Total	30

TREATMENT

The treatment of these patients consisted solely in the removal of the protein giving a positive reaction from the diet. The skin scarification method was used, and reactions were called positive only when a definite wheal measuring 0.5 cm. in diameter appeared. In the cured and improved cases, the improvement was noticed within the first week. In the apparently cured cases there has been no recurrence within six months, and in some cases one year, though they are taking small quantities daily of the foods to which they were originally sensitive. Skin tests performed six months later in six of the cured cases, gave negative results.

SUMMARY

Of seventy-eight cases of eczema tested with proteins, thirty gave positive skin tests. Like asthma, anaphylactic eczema occurs more frequently under the age of 30. Eczema associated with asthma or hay fever is usually anaphylactic. Only a small percentage of all eczema cases are anaphylactic, but it is essential that patients be thoroughly tested in order that they may be properly classified and treated.[4]

2 West Eighty-Eighth Street.

4. In addition to the references already given, the following will be found of interest:

Talbot, F. B.: Med. Clin. N. America **1**:985 (Jan.) 1918.

Walker, I. C.: Causation of Eczema, Urticaria and Angioneurotic Edema, J. A. M. A. **70**:897 (March 30) 1918.

Fordyce, J. A.: J. Cutan. Dis. **29**:129, 1911.

McBride, W. L., and Schorer, L. H.: J. Cutan. Dis. **34**:70 (Feb.) 1916.

Hoobler, B. R.: Tr. Am. Ped. Soc. **28**:188, 1916.

Schloss, O. M.: A Case of Allergy to Common Foods, Am. J. Dis. Child. **6**:341 (June) 1912; Tr. Am. Ped. Soc. **27**:62, 1915.

Haller, D. A., and Walker, I. C.: Syphilis with Neurologic Symptoms Simulating Other Conditions, J. A. M. A. **67**:1497 (Nov. 18) 1916.

Fisher, L.: New York M. J. **108**: 804 (Nov. 9) 1918.

ADENOMA SEBACEUM ASSOCIATED WITH A TERATOMA OF THE KIDNEY

REPORT OF A CASE *

E. D. CRUTCHFIELD, A.B., M.D.
GALVESTON, TEXAS

The occasional reference in literature to adenoma sebaceum associated with congenital tumors of the kidney or other abdominal viscera leads me to report this case of adenoma sebaceum with an associated teratoma of the kidney.

H. Goldenberg [1] has recently called attention to the frequence of adenoma sebaceum and various congenital tumors. Rosen and Wolf [2] have recently presented a case of adenoma sebaceum in a boy, aged 11, in which a history of the removal of a tumor of the kidney of the Wilm type was obtained. Lapowski [3] has referred to a case of adenoma sebaceum and peculiar tumors of the heart and kidney — not sarcomas—in the *Annales de Dermatologie et Syphiligraphie*, 1914-1915.

REPORT OF A CASE

History.—Stella J., a Caucasian woman, an American, aged 27, the mother of two normal children, whose mother and sister were living and well, and whose father and brother had committed suicide, presented numerous small, pinhead to split-pea sized nodular growths on each side of the nose, cheeks and forehead. The tumors were somewhat symmetrically placed and piled up in the nasolabial folds. The color varied from brown to red. She had marked associated telangiectasia and large coarse pored skin. The patient was mentally alert and of normal intelligence. She was unable to state when the lesions first appeared, but was sure they became more pronounced about puberty. Diagnosis: Adenoma sebaceum. Three weeks later she presented herself in the surgical service of Dr. A. O. Singleton with a temperature of 104 F., pulse 116, complaining of continuous pain in her left side, sweats, nausea and vomiting.

Examination.—The blood showed leukocytosis. The urine from the right ureter contained a little albumin and a few leukocytes; the urine from the

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* From the Department of Dermatology and Syphilology, University of Texas.

1. Goldenberg, H., in discussion on Rosen and Wolf: Adenoma Sebaceum, Arch. Dermat. & Syph. **1**:329 (May) 1920.

2. Rosen and Wolf: Adenoma Sebaceum, Arch. Dermat. & Syph. **1**:329 (May) 1920.

3. Lapowski, B, in discussion on Rosen and Wolf: Adenoma Sebaceum, Arch. Dermat. & Syph. **1**:329 (May) 1920.

left ureter contained much blood. Roentgen-ray examination showed the left ureter displaced toward midline. Examination revealed a tumor mass from the costal margin to the brim of the pelvis and extending to the midline anteriorly.

Necropsy Examination.—At necropsy a tumor of the left kidney was found strongly adherent to the diaphragm and lumbar muscles. Many vascular adhesions passed from the capsule of the tumor in all directions. The right kidney was also about four times its normal size and of about the same consistency as the tumor mass and strongly adherent posteriorly. Grossly, the tumor was twice the size of a child's head and of a doughy consistency. Microscopically, Dr. Henry Hartman found the tumor to consist of smooth muscle, fat and larger areas of sarcoma and reported the tumor a teratoma of kidney (Wilm type).

I am indebted to Dr. A. O. Singleton for the privilege of reporting these findings.

ERRATUM

In the August issue of the Archives of Dermatology and Syphilology the paragraphs beginning with "Dr. G. H. Fox," the third line from the top on page 262 and extending to the next case report "Melanoma Treated by Radium," should have followed the case report on "Dermatitis Herpetiformis" on page 264.

Editorial

TEACHING THE UNKNOWN

I once heard a philosopher say that "much time is wasted in learning what is not so." It has often occurred to me that this trite homily applies with special force to the teaching of dermatology. Who that has taught dermatology for many years but can recall many precious hours wasted in teaching what is unknown? This carries with it a double loss, for in addition to the loss of time to the teacher, the student is supposed to memorize much that is only of doubtful value, and dogmatic assertions concerning the unknown tend to unfit him for helpful individual inquiry.

The lack of exact knowledge of disease of the skin by the average family doctor is almost appalling. In speaking of this to a graduate of one of the foremost universities of this country, whose teacher was one of the Nestors of American dermatology, he openly admitted that while he had attended ————'s lectures and passed his examinations, still he knew nothing about dermatology. This confession from one of the most successful practitioners, himself a teacher of medicine, is a subject deserving of thought. One reason why dermatology is not a *pons asinorum* to medical students is that diseases of the skin were among the first to receive attention and much of the nomenclature of today goes back to the time of Hippocrates and to the reign of Darius II, king of Egypt. For two thousand years, therefore, they have been the objects of study, of painstaking observation and of record. What surprises us is that this accumulated knowledge does not give us a clearer insight as to the cause and cure of some of the diseases of the skin whose names indicate that they were known long before the circulation of the blood was discovered by Harvey and while epilepsy was considered to be due to the harboring in the body of "evil spirits." At the same time, I believe that the progress made and what is actually known in dermatology will compare favorably with that in other departments of medicine.

Another reason why the family doctor does not do justice to the patient with a disease of the skin, is that the subject of dermatology as taught in our leading medical schools is an exceedingly complex theme whose very nomenclature constitutes almost a language in itself.

To teach dermatology successfully so that the future medical man may have some definite knowledge of cutaneous manifestations and their significance and be able better to give relief or at least not to harm

the patient and to know his own limitations, the subject should be simplified and everything culled from it that the student has not time or inclination to master. Limit instructions, therefore, to the common things, the nature of which we are reasonably sure, and leave the bulk of dermatologic lore to be acquired by one who seeks advanced standing or aims to specialize in this subject.

In addition to this, I would strongly emphasize the importance of not teaching "what is not so." Recently I heard of a whole lecture given up to parapsoriasis to a class of third year students. It is better to endeavor to stamp on the mind the clinical picture of plain, well defined psoriasis and that we know nothing as to its cause and little of its amelioration and cure.

The teacher should bear this in mind and not confuse a receptive mind with doubtful or unknown things. Pemphigus may be cited as another example, because this venerable disease is now denied even an existence by some, and to all its cause and cure are as little known as when Galen called attention to its uncertain position in dermatologic nosology and Sauvages finally stamped it with his approval as a disease *sui generis,* as it is generally understood today. If the teacher is successful in the allotted time of most curriculums in impressing the student with simple, easily applicable and indubitable facts—leaving the doubtful legion of unknown things for them to unravel at some future time, he will accomplish all that our present knowledge vouchsafes, and in addition if his precepts and example have stimulated in his students the desire to seek the truth and to unravel some of the knotted skeins that the eye sees without understanding, he will have accomplished all that a successful teacher is supposed to attain.

W. T. C.

Abstracts from Current Literature

SOME OBSERVATIONS ON SYPHILIS OF THE CENTRAL NERVOUS SYSTEM. G. O. Scott and G. H. J. Pearson, Am. J. Syphilis **4**:201 (April) 1920.

The authors discuss the incidence, etiology, and type of syphilis of the nervous system. Special attention is given to the significance of the different laboratory findings and the associated clinical evidence. They report a series of 210 cases, which they classify according to the variations in the different laboratory findings.

They conclude:

1. The *Spirochaeta pallida* invade the central nervous system during the early part of the stage of generalization of syphilis.

2. On account of the great damage done by the *Spirochaeta pallida* to the central nervous system, if treatment of a neurosyphilitic is delayed, a proper diagnosis should be made and treatment instituted at the earliest possible date, namely, before clinical signs appear.

3. The only certain method of making this diagnosis when it will be of most value to the patient is by performing a lumbar puncture and examining the cerebrospinal fluid A lumbar puncture should be made on every patient with generalized, late and asymptomatic syphilis, on every patient with primary syphilis with a positive blood Wassermann reaction and on every patient with nervous disease. There is no reason why a lumbar puncture cannot be made in ordinary office practice.

4. If the serology does not indicate the presence of the *Spirochaeta pallida*, they do not advise treatment directed with special attention to the nervous system. They do not consider that the following findings in the cerebrospinal fluid indicate an invasion of the *Spirochaeta pallida* in an early case of syphilis without nerologic signs:

(*a*) Cells 0 to 7; globulin not increased; Wassermann reaction negative; colloidal gold curve, negative.

(*b*) Cells 0 to 7; globulin increased; Wassermann reaction negative; colloidal gold curve negative.

(*c*) Cells 0 to 7; globulin normal or increased; Wassermann reaction positive; colloidal gold curve, negative.

These cases should be watched with the greatest of care, but unless further indications appear at a later date, no other treatment than systemic is necessary.

5. If the serology indicates invasion of the central nervous system by the *Spirochaeta pallida*, they advise special treatment for the condition of the nervous system. They consider that the following serology findings indicate neurosyphilis, even though clinical neurologic findings are negative:

(*a*) Cells increased over 7; globulin not increased; Wassermann reaction negative; colloidal gold curve, negative.

(*b*) Cells increased over 7; globulin increased; Wassermann reaction negative; colloidal gold curve, negative.

(*c*) Cells increased; globulin normal or increased; Wassermann reaction positive; colloidal gold curve, negative or positive.

6. All patients with generalized, late or asymptomatic syphilis should be given a neurologic examination, for in a few cases of late degenerative neurosyphilis the clinical findings are positive, but serologic findings are negative. Neurologic findings are a guide to the treatment to be adopted.

7. If the stage of invasion by the *Spirochaeta pallida* is early, systemic treatment may be all that is necessary. If the stage of invasion is later or if neurologic signs are present, combined systemic and intraspinal treatments are a necessity.

8. Ogilvie's modification of the Swift-Ellis method is the most advantageous for the preparation of arsphenamized serum. There is no reason why intraspinal treatment cannot be given in ordinary office practice.

9. In cases of tabes with marked clinical signs, caution should be used in commencing intraspinal treatment on account of dangerous precipitation of symptoms.

TOMLINSON, Omaha.

PRENATAL SYPHILIS. JOHN A. KOLMER, Am. J. Dis. Child. **19**:344 (May) 1920.

The author makes a strong plea for the study and prevention of the disease in the prenatal period, and urges cooperation between dermatologists, pediatricians and obstetricians in the care and management of these cases before and after birth. Probably most can be done toward checking the spread of syphilis, and particularly its transmission to offspring, by subjecting prospective and potential parents to clinical, and especially immunologic, examinations for syphilis, and affording adequate treatment within the means of all, including the poorest of persons, seeking medical aid in our dispensaries.

It has been stated that a man ceases to be infectious within from two to five years after contracting syphilis, depending on the thoroughness of treatment, but that a woman may transmit the disease for an indefinite period; this is probably fallacious teaching in so far as the infectiousness of men is concerned. Fournier, for example, in a study of 142 men who contracted syphilis prior to marriage and infected their wives, found that twenty-eight, or about 20 per cent., were known to have been syphilitic for from five and one-half to eighteen years.

Kolmer believes that it is proper to regard all children as probably syphilitic when born of parents one or both of whom react positively to the Wassermann test, even though both the child and parents are clinically free of the disease. Congenital syphilis may manifest itself in so many different ways that the usual clinical picture carried in the minds of the majority of physicians, namely, the child presenting the appearance of "the little old man with a cold in the head" and blebs on the skin, serves for the clinical diagnosis of but a small percentage. As is well known, there may be no discernible lesions and symptoms, and all immunologic tests, such as the Wassermann and luetin tests, may be negative because so many prenatal infections are with treponemas of attenuated virulence inducing activity for several years after birth. As all evidence indicates that a persistently positive Wassermann reaction means presence of living treponemas in the body even in the absence of discernible lesions and symptoms, and since the possibility of transmission of these to offspring always exists, particularly from the mother with a posi-

tive Wassermann reaction, the author believes that the physician does well to regard with suspicion the offspring of such parents and even to institute specific treatment as a precautionary measure, especially if such children are manifestly below par in weight and nutrition.

Congenital syphilis should draw both obstetrician and pediatrist into closer professional cooperation, and constitutes an important reason for enlisting the services of the pediatrist in the care of the child before its birth instead of some weeks or months after. The obstetrician alone, and the prenatal clinic, by adequate treatment of the unfortunate parents, can do most in lowering the high but really unknown percentage of intra-uterine deaths of human beings who never had a chance for survival. The pediatrician can aid in this work if he is called in time and given an opportunity, and he may do much toward lowering infant mortality by bearing in mind the wide dissemination of syphilis among persons of marriageable age in both sexes, and the imminent danger of transmission to their offspring.

WAUGH, Chicago.

A VALUABLE METHOD OF EMPLOYING ARSPHENAMIN IN SYPHILIS. OLIVER S. ORMSBY, J. A. M. A. **75**:1 (July 3) 1920.

The author describes a modification of the so-called Pollitzer method of administering arsphenamin. In the early stage, before generalization has occurred three injections of arsphenamin are given with an interval of one day between the injections. The average dose is 0.4 gm., but in some instances 0.5 or 0.6 gm. are given if the patient is large and vigorous. In patients not previously treated the first dose is never more than 0.2 gm. Following this, one month's treatment with mercury, either by injection or inunction, is employed. Six weeks from the last arsphenamin injection, three more are given. In well developed cases not previously treated, the same procedure is employed, except that after the second series of arsphenamin twelve injections of mercuric salicylate are given at weekly intervals, or their equivalent in inunctions over a period of three months, when a third series of arsphenamin is given as before, this being followed by another three months of mercury. In the second year two series of treatment are given in the Wassermann negative cases as a prophylactic measure. In the Wassermann positive cases the procedure is as outlined for the first year.

Ormsby states that the method of treatment described in this communication proved efficient in a number of cases resistant to other methods. The absence of untoward results and reactions of any moment in the large number treated makes it appear as safe as other methods. It seems evident from experimental work herein reported that frequently repeated small doses, that is, from 0.1 to 0.15 gm., are inefficient. The combined use of arsphenamin and hydrargyrum in periods, either as herein described, or by the method commonly employed today in which arsphenamin is administered every five or seven days in series of from five to eight injections, appears at present to be the method of choice. The promptness with which many patients become clinically free and Wassermann negative, often after a single course, is encouraging, but should not lead to the conclusion that the disease is eradicated, as Wassermann relapses occur from six months to a year or more after continuous negative reactions have been obtained. It is therefore necessary to continue treatment for from one to two years, even though it may seem superfluous in some cases.

WAUGH, Chicago.

PELLAGRA IN EGYPT DURING THE WAR, COMMITTEE REPORT.

London Letter, J. A. M. A. **74**:1658 (June 12) 1920.

In 1918, owing to the presence in Egypt of a large number of prisoners of war suffering from pellagra, a committee was appointed to investigate the situation. It was found that the deficiency disease in this instance was due to insufficient assimilation of protein. The disease is characterized by erythema and pigmentation of the exposed parts of the body, on the back of the hands first, a fortnight later on the feet, these discolored patches being dry and not sweating even under pilocarpin administration. Profound disturbance of nutrition with early wasting of the muscles of the shoulder girdle, and progressively increasing fall of blood pressure follow. Loss of appetite is a very early symptom, and there is defective secretion of hydrochloric acid in the gastric juice. Herewith there is impairment of digestion, both gastric and pancreatic, malassimilation of protein and fat, and an increased bacterial growth in the intestines, with intermittent diarrhea leading to further loss of ingested, but incompletely absorbed, food. The enhanced destruction of protein gives very foul smelling stools and indican appears in the urine in increasing quantities; apathy comes on, perhaps melancholia, and the patient dies. Death is due to some intercurrent infection: pneumonia, dysentery, tuberculosis, and malaria accounted for 91 per cent. of deaths.

The important question was how this disease was to be prevented. Eighty-eight per cent. of the cases arose among newly captured Turkish prisoners, who for months had available only two thirds of their normal rations, and had suffered "from long continued undernutrition," as their German general had reported the year before. Further, the protein of their diet came mostly from wheat, barley or maize, very little from meat. Now Hopkins and Wilcox, in 1907, showed that the chief protein of maize cannot keep rats alive, as it does not contain enough tryptophan, an amino-acid of the aromatic series; in 1913, Sandwith suggested that want of tryptophan might help to cause pellagra. The committee had the help of Prof. W. H. Wilson of the Cairo School of Medicine, who has long been working at the different nutritional values of the proteins, which seem in part to depend on their individual amino-acids. For the making of epinephrin a benzene nucleus is essential. For the production of this the human organism depends on the hydrolysis of special proteins in the food supply, and even then the yield of tryptophan in this process may be broken up by an overwhelming bacterial flora in the duodenum. Every diet scale considers how much protein is necessary for the man of 70 kg., which is agreed to be 40 gm. daily. But that means grams absorbed, and for normal persons must be increased by one tenth; but experiment proved that for Turkish prisoners it required to be increased by one half, so that, even if they had received full rations, the Turks would have been underfed. But, further, they were fed on the wrong proteins. Wilson calculated the "biologic value of the proteins" (B. V. P.) of various foodstuffs, and found that, to replace 30 gm. of meat as protein supply in a man's diet, 34 gm. of rice protein were necessary, 50 of beans, 76 of bread, and 102 maize. Maize-eating people, therefore, suffer from pellagra because it has the lowest biologic value of the proteins of all the cereals, and if damaged or decayed it is all the less nutritious and pellagra arises more quickly. Vegetable proteins are not so easily assimilated as those in meat, and, further, the beans for the prisoners were not at first well cooked. These difficulties were all adjusted, but it was found that men might escape pellagra on a particular diet while resting, but suc-

cumbed as soon as they worked hard; so the diet for heavy labor, though showing already sufficient calory value and vitamin content, had to be increased; then the pellagra ceased.

WAUGH, Chicago.

A STUDY OF FOUR CASES OF BEGINNING SQUAMOUS-CELL CARCINOMA OF CORNIFYING TYPE. R. C. WHITMAN, J. Cancer Res. **5**:155 (April) 1920.

The lesions investigated appeared in verrucous keratoses and showed microscopically pearl formation and cells typically large and round with vesicular nuclei and abundant, opaque protoplasm. Associated degenerative changes in the corium were elacin, basophilic collagen and leukocytic infiltrate invading the cutis. The latter changes are frequently encountered in this type of carcinoma and are characteristic of senile skin.

CASE 1.—The patient had a cornifying carcinoma arising multicentrically from the basal and prickle cell layers of the epidermis and hair follicle with early stages of growth within the margins of the verruca not in themselves appearing malignant. The usual associated inflammatory reaction was absent.

CASE 2.—This patient presented a cornifying carcinoma arising diffusely from the germinal layer of the epidermis, characterized by "blue areas" of degenerated collagen, elacin degeneration of deep lying elastic tissue, inflammatory changes of contiguous corium, as shown by dense deep cellular infiltration and vascular changes and, among the epithelial features, a bud of proliferating epithelium apparently arising from the basal layer and hair follicles and presenting a disorderly arrangement of large spindle-shaped cells with large pale vesicular nuclei containing deep staining nucleoli.

CASE 3.—A cornifying carcinoma arising diffusely from the basal layer only and presenting on section interruption and degeneration of basement membrane, basophilic collagen invaded by acanthotic epithelial pegs, absence of wandering cells, changes in the basal layer represented by intensification of staining and enlargement of individual cells, ramifying and proliferative growth and formation of numerous small epithelial pearls and keratinized channels of epithelial structure surrounding blood and lymph vessels.

CASE 4.—This patient presented a cornifying carcinoma arising diffusely from the prickle cell layer only in which the malignant growth was within an intact basal layer which in places surrounded the proliferating cells in a glandlike arrangement. The epidermis showed acanthosis, abundant mitoses confined to the prickle cells, atypical cellular growth and formation of malignant buds. The corium showed elacin, basophilic collagen, eosinophilic infiltrate and a vacuolated hyaline coagulum in places replacing the basement membrane.

In a discussion of theoretical considerations the writer upholds the hypothesis that the cancer cell is a mutated somatic cell and shows the impossibility of a tumor being produced through the reversion of a mature cell to an embryonic stage of development.

The preceding study of the four cases of carcinoma of the same general type, no two of which are exactly alike in the details of origin and growth, is regarded not as a reason for assuming the result of adaptation to differences of environment, but for believing that the differences of behavior are proof of corresponding differences in the inner structure and life of the cell.

The tumor cell is defined as a cell arising by mutation from a normal somatic cell existing normally in the tissues, or displaced as a cell rest, and usually retaining enough of the properties of the parent cell to render its point of origin recognizable. Mutative changes are thought to be favored by hybridization and mongrelization and brought about by such chronic irritations as excite, over a long period, constantly renewed and constantly defeated efforts at repair.

Recurring mutations in a growing tumor bring about a progressive loss of the original character of the mother cell, explaining the lack of uniformity in the biologic properties of a carcinoma and the difficulty in recognizing histologically the real beginning of a carcinomatous process.

H. R. FOERSTER, Milwaukee.

TOXIC JAUNDICE IN PATIENTS UNDER ANTISYYPHILITIC TREATMENT. C. V. BAILEY and A. MACKAY, Arch. Int. Med. **25**:628 (June) 1920.

It cannot be recognized before treatment which patients are susceptible to arsenic toxemia, either early or late, although urinary examinations should always be made previous to the use of arsphenamin.

The writers examined the blood and urine in twenty-five cases of toxic jaundice following antisyphilitic treatment, and in fifteen cases of other diseases. The toxic period had varied from sixteen to 136 days, but no patient had signs of nephritis. The treatment had consisted of synchronous injections of mercury and novarsenobenzol (Billon), repeated at seven day intervals.

No arsenic was found in the urine of any of these patients and all urines were free from protein and pathologic sediment. Bile pigment was found in the plasma in eleven cases, and oxidative activity in the urine was low in the severe liver cases. Hypercholesterolemia was found in nearly all the toxic cases and seemed to be an early sign of toxic jaundice. Carbohydrate metabolism was normal. Blood urea nitrogen and uric acid were generally increased.

The authors state that exercise should be carefully regulated as it tends to have a deleterious effect on debilitated patients. They are also led to believe in a rich carbohydrate diet, very low in fat and protein. This diet should be instituted before treatment is begun and continued throughout its course. Delayed poisoning by arsenic is explained by the decrease in excretory powers of the kidneys, increase of the waste products in the blood, lowered resistance of the liver to toxins and an increase in the diet proteins.

JAMIESON, Detroit.

WIE IST DIE RADIKALE FRUEHHEILUNG DER SEROPOSITIVEN PRIMAR UND DER FRUEHSEKUNDAEREN SYPHILIS AM SICHERSTEN ERREICHBAR? (HOW CAN THE RADICAL CURE OF PRIMARY AND EARLY SECONDARY SYPHILIS BE BEST ATTAINED?) HABERMANN and SINN, Dermat. Zeitschr. **29**:321, 1920.

The patients who have passed the negative Wassermann phase of primary syphilis are best treated by two or three courses of arsphenamin (in the practice of the authors, neosalvarsan, sodium salvarsan and silver salvarsan) and mercury. A single course, even if the Wassermann reaction becomes negative, is not sufficient and the patient is not entirely cured, as is proved by the occurrence of the relapse syndromes. The course consisted of the injection of from eight

to ten doses, beginning with 0.3 gram and ascending to 0.6 gram, at intervals of from five to seven days. Gray oil was administered unless counterindicated. A period of from six to eight weeks constituted the rest interval. The second course was given even if the Wassermann reaction had been persistently negative during treatment. The authors found their patients free of symptoms clinically and serologically for a year or longer after this two course therapy. Although they have not had opportunity to study the spinal fluid, they believe from the clinical study of the patients that cerebrospinal involvement was not present. Patients with chancre, who do not give a positive Wassermann reaction at any time, may do without the second course, although the writers are reluctant to forego the "safety" course even in these patients. Mercury is thought to be an essential part of the cure of syphilis and should be used in the treatment of the disease. Arsphenamin alone may suffice in the prophylaxis of syphilis if no symptoms are manifest, as in a wife of a known syphilitic, etc.

GOODMAN, New York.

COCCIDIOIDAL GRANULOMA, INCLUDING THE FIRST REPORTED CASE EAST OF THE MISSISSIPPI. KENNETH M. LYNCH, Southern M. J. **13**:246 (April) 1920.

Lynch reports an unusually interesting case of coccidioidal granuloma in a colored woman who, admitted to the hospital in a delirious condition which lasted until death, was thought to have tuberculosis. The illness had begun about two months before the patient was seen, when a severe attack of supposed influenza developed. The patient was in bed for three weeks, and was then up for two weeks, but was unable to do any work. She again returned to bed, where she remained until death. On her entrance to the hospital her pulse was weak and its rate 136, respiration 44 and temperature normal. The patient showed extreme emaciation; râles and areas of consolidation were found at the apex of the right lung, and a lesion described as a bedsore was present on the right buttock. Death occurred three days later.

Necropsy aroused some doubt as to the correctness of the diagnosis of tuberculosis. Gross necropsy findings were recorded as several empty cavities in the apex of the right lung, with complete but delicate encapsulation and no surrounding tubercle formation, some toughness and emphysema of the lung generally, edema of the lungs, parenchymatous degeneration of the heart and acute nephritis.

Lynch, following a hasty examination of a microscopic slide was about to pass the case as one of tuberculosis, but he noticed a peculiar body within a giant cell, and on further study was able to identify this as coccidioides immitis and to discover many of the parasites, as well as miliary lesions, in the liver, spleen, pancreas, kidneys and lungs.

While the lung lesions resembled tuberculosis rather closely, the vascularity, the lack of focal organization as tubercles, the character of the giant cells and the lack of multicellular necrosis, particularly of caseation, seemed to furnish differentiation.

The author believes that the atrium of infection was the lung, where the apparently oldest lesions were found, while other organs were involved through hematogenous spreading.

In examining the literature Lynch finds that sudden onset, much like the acute febrile diseases, has been seen in some cases of this disease, while in others the onset has been so gradual that the patient was not aware of his

illness. In concluding his report, the author suggests that cases of uncertain tuberculosis in which the organism cannot be found, should be examined for this or kindred infection.

SENEAR, Chicago.

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. JOHN A. KOLMER and TOITSU MATSUNAMI, Am. J. Syphilis **4**:278 (April) 1920.

This is a report of a study of several hemolytic systems used to conduct complement-fixation tests in syphilis: (1) to determine their relative delicacy, and (2) to determine the influence of natural antisheep hemolysin in human serums. The authors conclude:

1. With the technic employed, comparative complement-fixation reactions with 503 serums from syphilitic persons under treatment have shown that tests conducted with antihuman and antichicken hemolytic systems were somewhat superior in sensitiveness to those conducted with antisheep and antiox systems.

2. From 2 to 10 per cent. more serums from syphilitic persons react positively in an antihuman system than in an antisheep system.

3. An antiox hemolytic system is more sensitive than an antisheep system yielding from 2 to 5 per cent. more positive reactions with the serums of syphilitic persons.

4. Antihuman and antichicken hemolytic systems are of about equal sensitiveness in complement-fixation tests with heated human serums.

5. The differences in delicacy of reactions conducted with antisheep, antihuman and antichicken hemolytic systems were more apparent in tests conducted with 0.01 to 0.001 c.c. of each serum than in tests conducted with 0.1 c.c. serum.

6. Natural hemolysins in human and guinea-pig serums, and particularly antisheep hemolysins, reduced the delicacy of complement-fixation tests conducted with an antisheep hemolytic system after the method described, particularly if the results were read after the tubes had stood for sixteen hours or longer in a refrigerator; antihuman and antichicken hemolytic systems were more sensitive and served to detect smaller amounts of syphilis antibody in human serums.

TOMLINSON, Omaha.

ZWEI FAELLE VON "FOX-FORDYCES KRANKHEIT (TWO CASES OF "FOX-FORDYCE DISEASE"). C. RASCH and A. KISSMEYER, Dermat. Ztschr. **29**:196 (April) 1920.

The authors give a summary of the literature with reports of all cases heretofore reported by Fox, Fordyce, Haase, Withers and others as a rare papular disease affecting the axillary region. They report two new cases of this dermatosis which may be included in the group of "neurodermite chronique circonscrite" of Brocq. One of the cases was that of a woman of 33 who had suffered from intolerable itching of the axillae, pubes and areolar of the mammae for ten years. The second patient was a woman of 24 who four years previously noted the itching papular eruption of the axillae, pubes and areolar mammae. Only regions with adult hair growth are affected, lanugo hairs being free. The papules of the disease are perifollicular, conical, brownish or reddish brown in color. In the second case many hairs had been destroyed. The area about the disease is lichenified. The itching is intense and in the younger woman required opiates.

Treatment with roentgen ray was not promising.

The microscopic picture revealed a hyperkeratosis, parakeratosis and acanthosis with infiltration of large epithelial cells in the corium. The hypertrophy of the rete malpighi was especially marked about the hair follicles and the excretory system of the sweat apparatus. In the corium there was an infiltration about the hair follicles and sweat ducts which appears to be characteristic of the affection, although Rasch notes that he has observed a similar condition in another disease attended by intense itching, namely, "prurigo nodularis."

The writers intend to use filtered rays in an effort to cause atrophy of the hair follicles and sweat ducts with the hope of curing the condition.

GOODMAN, New York.

PRURITUS VULVAE: ITS SIGNIFICANCE AND TREATMENT. P. BROOKE BLAND, Therap. Gaz. **36**:3 (March) 1920.

Pruritus vulvae is not a specific entity but a manifestation of some local or systemic affection. The etiology of the condition may be classified under physiologic and pathologic etiology. The pathologic causes depend on local or systemic disease. The most common physiologic condition associated with pruritus is menstruation. Pregnancy, however, is the most common physiologic cause.

Systemic causes in order of frequency are: glycosuria, diabetes, nephritis, acidosis, neuroses, auto-intoxication and endocrine dysfunction. Local causes are: excessive acidity of the vaginal secretion, profuse leukorrheal discharge, purulent discharge, highly acid urine, uncleanliness and foreign body irritation. In fact all local lesions of the vulva productive of irritation are constantly associated with pruritus. Seligman claims to have isolated a diplococcus in the so-called idiopathic cases.

Four distinct skin lesions occur in pruritus: first, superficial desquamation with ulceration; second, hyperplasia or fibrosis; third, atrophy or sclerosis; and fourth, discoloration.

The milder cases, the author states, are cured by the removal of the cause and local cleanliness. In the more violent types the vulva is shaved and then scrubbed with a coarse cloth saturated with 2 drams of tincture of green soap in a quart of warm water. The scrubbing should be continued for two or three successive days. The external parts are then given a generous painting with pure tincture of iodin. The vulva is then washed vigorously with tincture of green soap every morning and evening. After washing, the parts should be dried thoroughly and a 3 per cent. solution of iodin in albolene applied. In addition, the patient is told to use an alkaline douche twice daily.

LEVIN, New York.

DE L'INFLUENCE DES TRAITEMENTS INSUFFISAMMENT ACTIFS SUR L'APPARITION DES SYPHILIS MENINGES (THE INFLUENCE OF INSUFFICIENTLY ACTIVE TREATMENT ON THE DEVELOPMENT OF MENINGEAL SYPHILIS). MARCEL PICARD, Paris méd. **10**:211, 1920.

Picard, granting the existence of two strains of *Spirochaeta pallida*, with predilection for the skin and nervous system, respectively, thinks it possible that a dermatropic strain may be changed into a neurotropic. Not only insufficient treatment, but also active treatment may favor syphilitic attack on the nervous system, if the dosage has been too small, the series too short, or if

there has been too long an interval between courses. The treatment is active enough to prevent the appearance of cutaneous accidents, and to cause the spirochetes to move toward the nervous system, where they are less vulnerable. It is because of this mechanism that we have seen so many accidents resulting in nervous diseases, ocular paralysis, etc., following the first therapeutic attempts with 606, but this therapeutic neurotropism appears possible after mercurial as well as after arsenical therapy.

He concludes: From the point of view of neurotropism, the little active agents, the benzoate, biniodid and pills are dangerous; small doses of strong therapeutic agents are dangerous; single series or long intervals between treatment with active agents are dangerous. At the beginning of syphilis, the treatment should be intensive and the therapeutic agent used in doses surely spirocheticidal. After the first treatment the rest period should be short, and treatment should be continued until clinical signs, blood serum and spinal fluid are negative.

SENEAR, Chicago.

PLEURALITY OF SPIROCHETES OF SYPHILIS. P. PAGNIEZ, Presse méd. **28**:266 (May) 1920.

Pagniez believes that the researches of Levaditi and others lend plausibility to the view that the syphilitic spirochetes which produce cutaneous manifestations—the dermatropic—and those which produce paresis—the neurotropic—are different strains. In favor of this view he adduces the following facts:

Animals that have been inoculated with one strain will show a chancre when inoculated with the other strain.

The dermotropic strain after passage through rabbits continues pathogenic for monkeys; the neurotropic strain, on the other hand, after a single passage through a rabbit loses its virulence for monkeys.

A rabbit after recovery from a chancre from the dermotropic strain was inoculated in one testicle with the dermotropic strain and in the other with the neurotropic strain. The dermatropic inoculation did not develop, while the neurotropic strain developed a chancre.

In animal experiments the incubation period of the dermotropic strain was about six weeks; that of the neurotropic, four months.

The lesions produced by the two strains were of different character.

KETRON, Baltimore.

LES ACRODERMATITES SUPPURATIVES CONTINUES (CONTINUOUS SUPPURATIVE ACRODERMATITIS). E. BODIN, Paris méd. **10**:185 (March) 1920.

In this instructive and exhaustive paper Bodin discusses the subject of chronic suppurative acrodermatitis: the clinical course and appearance of the eruption, its differential diagnosis, etiology and pathologic anatomy and treatment are considered in detail.

He finds that from the ordinary pyodermatitis of the fingers it may be distinguished by the successive attacks of pustules, their arrangement in sharply defined patches without neighboring isolated lesions, the absence of lymphangitis and adenitis, and the characteristic course of the malady. The fact that the primary lesion is pustular rather than vesicular differentiates it from ordinary and ringworm eczema. The characteristic vesicles, the location on the lateral surfaces of the fingers and the evolution of the eruption seen in

dyshidrosis usually prevent difficulty. Dermatitis repens offers the greatest difficulty in diagnosis, but the preceding injury and the characteristic spreading margin distinguish this disease. Bodin compares the characteristics of chronic suppurative acrodermatitis with those of dermatitis herpetiformis and finds that cases of the latter, limited to the extremities, have many points in common with the former disease.

In discussing etiology, Bodin finds evidence to show that the two common theories, i. e., origin from staphylococcus infection or from a trophoneurosis, are not tenable. He believes that chronic suppurative acrodermatitis is related to certain localized types of dermatitis herpetiformis. In support of this theory he offers the following facts: coincidence of the two diseases in two cases of Carle's, the appearance of extensive, polymorphous, erythematous pustular eruptions in cases of acrodermatitis; the beginning of the disease by a persistent and localized erythema; the itching, prickling, burning and shooting sensations; the occurrence of successive attacks and the general good health of the patient.

Bodin recalls that nearly everything has been used in the treatment of the disease, and states that he has had the best results from applications which are protective and mildly antiseptic, while radiotherapy has been of value in rebellious cases.

SENEAR, Chicago.

THE ACTION OF MERCURY OXYCYANATE ON THE WASSERMANN REACTION. IRVING SIMONS and R. L. JONES, Urol. & Cutan. Rev. **24**:6 (June) 1920.

The authors studied the action of mercury oxycyanate, administered by deep injection, on the blood serums of sixty-six syphilitics who showed strongly positive Wassermann reactions. Nearly all of them were in the late tertiary or latent stage of the disease. Some of the patients received treatment and Wassermann tests during a period of sixteen months. The average duration of treatment was 5.9 months. Good results were obtained in twenty-one cases; fair results in seventeen cases. For practical purposes one could combine these results and say that an adequate result was obtained in thirty-eight cases (57.5 per cent.). In the twenty-one cases in which good results were obtained, it required an average of 14.17 c.c. of a 1 per cent. solution of mercury injected during 2.6 months to produce a negative Wassermann reaction. These cases were then treated for two additional months, receiving totally an average of 29.94 c.c. of mercury in order to render the Wassermann reaction thoroughly negative. Comparing this with the results obtained with the arsphenamin preparations it would seem that this mercurial preparation is unusually potent. Mercury oxycyanate has few untoward effects and can be given intravenously as well as intramuscularly.

LEVIN, New York.

CONSIDERATIONS SUR LA PHYSIOLOGIE PATHOLOGIQUE ET LA PATHOGENIE DE L'URTICAIRE (OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY AND PATHOGENICITY OF URTICARIA). A. LOUSTE, Paris méd. **10**:198, 1920.

Louste, who is led to believe that all cases of urticaria whether of external or internal origin are due to anaphylaxis, discusses the various theories advanced as to the rôle of the blood, blood vessels, nervous system, etc., in the production of the eruption.

He states that the studies which he has just reviewed allow urticaria to be considered as an expression of anaphylaxis. It seems to result from the introduction into the organism, by various routes, of heterogeneous substances of which the albuminoids are best known. Under the influence of these different substances, which have been demonstrated in the blood serum and in the urine, the cells of the organism react with marked intensity, but in a fashion relatively identical. There is a more or less intense shock of the nervous system, with hemoclasic shock, and peripheral manifestations; itching, placque formation, edema of mucous membranes, accompanied or not by various phenomena such as dyspnea, diarrhea, albuminuria, etc.

The author then reviews the three theories explaining the mechanism of anaphylaxis; the chemical theory of Richet, the biologic theory of Friedländer, and the physical theory of Besredka, Wassermann and others.

The various methods of treatment are likewise reviewed.

SENEAR, Chicago.

FORDYCE'S DISEASE AS PSEUDO-KOPLIK SPOTS, AND A CAUSE OF MISTAKES IN THE DIAGNOSIS OF MEASLES. JOSEPH C. REGAN, Am. J. Dis. Child. **19**:455 (June) 1920.

Fordyce's disease is a chronic disease of the mucous membrane of the mouth and lips, which is characterized by the presence of whitish or yellowish, scanty or abundant, discrete, aggregated and often coalescent miliumlike bodies, occurring more especially on the inside of the mouth, laterally along the line of the teeth as far back as the last molar, and possibly somewhat less frequently on the vermilion or mucous and inner surface of the lips. The lesions are from pinpoint to pinhead in size, and are usually a pale buff or oatmeal color.

Fordyce spots are often mistaken for Koplik spots when they exist in patients developing German measles, and in patients ill with various contagious diseases and exposed to measles.

Well marked cases of Fordyce's disease are unusual in young children; the disease is most commonly seen in young adults and older children.

A differential diagnosis between Fordyce spots and Koplik spots is not difficult if the mouth is examined in sunlight—or at least daylight, and the color, arrangement, distribution, evolution, size and location of the lesions taken into consideration. In a few cases Koplik spots and Fordyce spots were seen together; their appearance is entirely different.

OLIVER, Chicago.

THE IMPORTANCE OF INTERNAL TREATMENT IN DERMATOLOGY. THE USE OF CACODYLATE OF SODA IN LARGE DOSES AND OF SODIUM HYPOSULPHITE. P. RAVAUT, Presse méd. **28**:73 (Jan. 28) 1920.

Ravaut believes that in the epidermophytic dermatoses the question of "soil" is an important one. Given a number of persons exposed in a similar way, and some will become affected with parasitic or fungous diseases of the skin, while others will escape. He does not believe that this is due to any special cutaneous sensibility, but rather to modifications of the body fluids or visceral alterations. He says that he has observed the disappearance of parasitic dermatoses after the administration of internal treatment alone. He reports over eighty-five cases of eczema in which the patient had received from 30 cg. to 1 gm., every one to three days, of a 10 per cent. solution of

sodium cacodylate intravenously administered. The course of treatment lasted three weeks, and a total of from 15 to 20 gm. of the drug were used. The results were uniformly good, the drug being well tolerated. Excessive pigmentation occurred in one case of Duhring's disease. Sodium hyposulphite by mouth seemed to relieve quickly the anaphylactoid erythrodermias following the administration of arsphenamin. A solution of the drug, in 20 per cent. strength, in doses of from 4 to 15 grains daily, was injected intravenously with good results in cases of erythema, urticaria, furunculosis, eczema and dermatitis artefacta. One case of tinea versicolor disappeared without external treatment. A case of cervical trycophytosis improved rapidly.

BECHET, New York.

A METHOD FOR DEMONSTRATING SPIROCHAETA PALLIDA IN REGIONAL LYMPH GLANDS. EDWIN W. SCHULTZ, J. A. M. A. **75**: 176 (July 17) 1920.

Schultz describes a modification of the method usually employed in securing material from lymph glands for dark field examination. He claims that merely puncturing the gland and making suction with the syringe without first injecting a small amount of fluid, gives comparatively poor results. By using the method as described, he has found *Spirochaeta pallida* in practically every case of untreated syphilis. A 2 or 5 c.c. hypodermic syringe with a sharp needle is employed. Into the syringe is drawn from 0.5 to 1 c.c. of sterile physiologic sodium chlorid solution. The gland is firmly fixed between the first two fingers and thumb of the left hand, and with the syringe in the right hand the needle is passed through the overlying skin and then gently through the capsule of the gland. The point of the needle is then rotated in order to break down some of the gland tissue. After this has been done, the saline solution is slowly injected into the gland, and the capsule swelling under the finger is noted, after which the point is rotated a few times more. Suction is then made with the plunger of the syringe and as much as possible of gland-pulp mixture is withdrawn, a few drops being generally quite sufficient.

WAUGH, Chicago.

CONTRIBUTION A L'ETUDE DU XANTHOME PAPULEUX GENERALISE (CONTRIBUTION TO THE STUDY OF GENERALIZED PAPULAR XANTHOMA). L. SPILLMAN and WATRIN, Paris méd. **10**: 193, 1920.

Spillman and Watrin regard xanthelasma, xanthoma tuberosum and xanthoma diabeticorum as clinical variants of a single disease. After reviewing the characteristics of the various types, they report an interesting case of generalized papular xanthoma occurring in a girl of 9 years. The patient suffered with polyuria with polydipsia, while the blood serum showed an increase in the cholesterin content. The interesting features in the case were the multiplicity of lesions, the marked diminution in the elimination of urea and the hypercholesterinemia.

After histologic study of the case, the authors feel that in their case a functional defect of the liver produced the hypercholesterinemia, and likewise an insufficient oxidation of fats, but they cannot support Chauffard and Grigant in their view that the excess cholesterin attacks the connective tissue cells of the derma.

They suggest that treatment in the widespread cases must of necessity be of a general nature, since the multiplicity of the lesions makes local treatment difficult, and they feel that a regimen directed toward the reduction of cholesterin offers the most hope.

SENEAR, Chicago.

LYMPHOCYTES AND CANCER IMMUNITY. FREDERICK PRIME, J. Cancer Res. **5**:105 (April) 1920.

The experiments were carried out with rats rendered immune to Flexner-Jobling rat carcinoma by previous inoculation, rats resistant to this tumor and rats resistant to Jensen rat sarcoma. The treated rats were given unfiltered roentgen rays from a Coolidge tube on five consecutive days for a total of 10 Holzknecht units.

Total white and differential blood counts were made before commencing the exposures, two days after the last exposure and subsequently at frequent intervals. Forty-eight hours after the completion of the last roentgen-ray exposure all the animals were inoculated with Flexner-Jobling rat carcinoma (or Jensen sarcoma). An enormous reduction in the lymphocytes, which in most cases remained low for a longer period than required for an inoculation "take," was obtained by the irradiation.

These experiments, carried out with a larger number of animals, carefully controlled, results duplicated and sources of error eliminated, proved definitely that a marked reduction in the circulating lymphocytes was not followed by any appreciable decrease in the immunity of these animals to tumor inoculation.

H. R. FOERSTER, Milwaukee.

KLINISCHER BEITRAG BETREFFEND DIE BEZIEHUNG VON HYPOTHYREOSE ZU DYSTROPHISCHEN VERAENDERUNGEN DER HAUT (RELATION OF HYPOTHYREOSIS TO DYSTROPHIC CHANGES OF THE SKIN). FRIEDERICH FISCHL, Dermat. Ztschr. **29**:201 (April) 1920.

Fischl gives a list of diseases that either through clinical evidence or through theoretical reasoning are caused by malfunction of the internal secretion of the thyroid gland. He reviews the contributions of last decade on the relation to the glands of internal secretions and the skin, with emphasis on the thyroid.

He reports a case in which inflammation of the thyroid accompanied typhoid. The skin of the entire body of the patient became grayish, distinctly thinned, cool, dry, and because of the atrophy of the subcutaneous fat, easily lifted from the underlying structures. The hair had become thin and areas of baldness were evident. The nails had become brittle and furrowed. Twelve teeth had been lost during the preceding three months. Thyroid medication was followed by marked improvement in the general condition and the skin improved in thickness, color and resilience. The nails lost their brittleness.

The case is thought to be exceptional in that the skin and adnexa alone were affected, and that edema and concomitant evidence of hypothyroidism were absent.

GOODMAN, New York.

EFFECT OF THERAPEUTIC DOSES OF MERCURY ON THE KIDNEYS AND THE DURATION OF ITS EXCRETION. L. G. Beinhauer, Am. J. Med. Sc. **159**:897 (June) 1920.

Mercury is detected by means of copper dust in an acid solution of the material tested, the copper taking up all mercury. The compound is collected, dried and heated, the vaporized mercury being deposited as an amalgam in a small particle of gold leaf.

The patients were thoroughly examined to exclude any possibility of previous mercurialization and suitable patients were given, serially, doses of calomel, ¼ grain every fifteen minutes, the total amount varying from ¼ grain to 2 grains. It was found that the excretion began from six to twelve hours after ingestion and may continue for six days if the dose is sufficiently large. The rate of excretion is the same for large and small doses, the kidneys not being injured during the process although many analyses of the urine showed temporary traces of albumin and a few hyaline casts.

Jamieson, Detroit.

RHINOPHYMA. M. G. Seelig, Surg., Gynec. & Obstet. **30**:394 (April) 1920.

Seelig describes the clinical features of rhinophyma and quotes the pathologic description from Dr. Martin Engman's forthcoming book on "Diseases of the Skin": "Rhinophyma is a familial disease representing some type of hereditary transmission. It occurs usually in the seborrheic type of individual. . . . The future rhinophyma subject shows a tendency toward flushing of the face on entering a warm room, after meals or under excitement. This flushing leads in time to chronic congestion, with secondary chronic infection of the skin of the nose and sometimes of the cheeks. This in turn leads to a chronic productive inflammation with vascular dilation, connective tissue formation and dilatation of the sebaceous glands into cyst formations. There is a marked thickening of the cutis vera, which throws the skin into folds and furrows. The end-result is the multiple formation of knobs or tumor-like masses."

The treatment is exclusively operative.

Goodman, New York.

A CASE OF EXTRA-MAMMARY PAGET'S DISEASE OCCURRING IN THE AXILLA, ASSOCIATED WITH CONDYLOMATA ACUMINATA IN THE EXTERNAL GENITALIA. Y. Satani, Brit. J. Dermat. & Syph. **32**:117, 1920.

Satani's patient was a man, aged 74, who had for six years had a patch of Paget's disease in the right axilla, which had been preceded by a wart in this location. In addition, the penis and scrotum were the site of an extensive growth of condylomata acuminata, which had developed some five years previously on some erosion of the penis. The entire patch of Paget's disease was excised and recovery was complete. The condylomata were treated successfully with roentgen rays and local applications.

The results of a histologic examination of the axillary lesion were compared with the findings in a case of mammary Paget's disease examined before and after radium treatment. As a result of this examination Satani concludes that Paget's disease may originate from any epithelial cell in loco;

local epidermis, sweat or sebaceous glands. He cites the occurrence of the disease in various parts of the body as evidence that the origin of the disease depends only to a slight extent on the specific structure of the local skin.

SENEAR, Chicago.

CALOR DE FIGO (TINEA ALBIGINA). E. VON BASSIEWITZ, Arch. Rio-Grandenses Med. **1**:55, 1920.

"Calor de figo" is the common name given to a dermatomycosis of chronic evolution often seen in the country districts of Rio Grande do Sul (Brazil). This dermatosis affects the colored races, and as a rule remains localized to the soles of the feet and the toe nails, although sometimes it involves the hands. Its principal characteristics are: hyperkeratosis with deep fissuring, achromia and keratoid onychia. The patients complain of intense pruritus and pain. The author has isolated a fungus (trichophyton?) which he has been unable to classify. The disease is similar to that observed by Jeanselme in Cochinchina under the name of Khi-Huen. Nieuwenhuis has observed in Java a dermatomycosis the clinical appearance of which is much like that of "calor de figo." He describes it under the name of tinea albigena.

PARDO-CASTELLO, Havana.

THE USE OF STOCK OR AUTOGENOUS VACCINES IN THE TREATMENT OF FURUNCULOSIS. A. MAUTÉ, Presse méd. **28**:64 (Jan. 24) 1920.

Mauté divides the vaccine treatment of furunculosis into two phases, curative and preventive. In the curative phase, he employs stock vaccine. When rapid results are desired, he injects intravenously ten million staphylococci on the first day, fifteen million on the second day, and twenty million on the third day. Two days later a second injection of twenty million is made. Immediate results are far superior with the intravenous method than with the subcutaneous. In the preventive phase, he uses an autovaccine consisting of five hundred million cocci to 1 c.c. in the following doses: first injection, 0.5 c.c.; second, three days after the first, 1 c.c.; third, four days after the second, 1.5 c.c.; fourth, five days after the third, 2 c.c.; fifth, five days after the fourth, 2 c.c.; sixth, seven days after the fifth, 2 c.c.

BECHET, New York.

THE MEDICAL AND SOCIAL CARE OF SYPHILIS AT THE WASHINGTON UNIVERSITY DISPENSARY. RICHARD S. WEISS and ADOLPH H. CONRAD, Am. J. Syphilis **4**:253 (April) 1920.

This article reveals the workings of a well-conducted clinic for the handling of syphilitic patients. Three factors were considered from the standpoint of efficiency: (1) the aspect of the problem from the public health standpoint; (2) the reaction of the patient and his family to the measures used for their own protection, health and comfort; (3) the clinical results of treatment. Of these three, the first is considered most important.

Numerous forms showing the patient's history, record of treatment, "follow-up" activities, etc., accompany the article.

TOMLINSON, Omaha.

FURTHER OBSERVATIONS ON THE PRESENCE OF ARSENIC IN THE SPINAL FLUID. George W. Hall, Russell J. Callender and Edward S. Holmblad, Arch. Neurol. & Psychiat. **3**:631.

For these experiments the authors chose patients who had not previously received any form of intravenous medication. Eighteen patients were given the treatment. Serum from the patient's blood was injected into the spinal canal, and at intervals of from four to eleven hours after an arsenical preparation was given intravenously. At different intervals after the intravenous injection, the spinal fluid was withdrawn and tested for arsenic.

No attempt was made to estimate quantitatively the amount of arsenic present. The experiments were made in an attempt to develop a safer and more effective method than the Swift-Ellis.

The authors concluded that arsphenamin given intravenously in 0.6 gm. doses might be detected in the spinal fluid in from 25 to 35 per cent. of cases, and that irritation of the meninges by the injection of autoserum into the spinal canal does not increase this percentage.

Oliver, Chicago.

DAS ERSTE JAHR DES BESTANDS DER ANSTALT FUER KRAETZE-SCHNELLKUREN IM WILHELM INENSPITAL (EXPERIENCES SCHNELLKUREN IM WILHELMINENSPITAL (EXPERIENCES TREATMENT OF SCABIES IN WILHELM HOSPITAL, VIENNA). Moritz Oppenheim, Wien. klin. Wchnschr. **33**:102, 1920.

The incidence of scabies having increased greatly, and ordinary methods of treatment being found too time consuming, a "rapid" treatment was begun at the Wilhelm Hospital which takes only three hours. About 12,000 patients have been treated, with few recurrences. The patient is stripped and thoroughly smeared with soft-soap for fifteen minutes. A bath at 30 C. follows, during which soft-soap is rigorously brushed into the skin, especially the points of predilection of the burrows. After the bath the patients are dried, and sulphur (Hardy's formula or one of its modifications) is employed. The patient is then wrapped in sheets and the hands and feet are gloved for two hours, after which another bath follows, and the salve is washed off with soap. Drying and anointing with zinc salve complete the cure. The clothes are sterilized by dry heat.

Goodman, New York.

FIBROMA SIMPLEX. Louis Savatard, Brit. J. Dermat. & Syph. **32**:378, 1920.

Savatard describes a tumor appearing on the upper arm of a young girl. The lesion was small, slightly raised above the skin surface and movable with it, its surface being smooth and the color reddish brown. The tumor, which was extremely hard, had been present for three months.

Microscopically the tumor consisted almost entirely of spindle-celled fibrous tissue, with numerous smooth muscle fibers at the periphery. The growth caused a thinning and stretching of the papillary body, and the hair follicles and sebaceous glands were pressed aside.

Senear, Chicago.

SEROLOGIC RESEARCHES IN PRIMARY SYPHILIS. Clément Simon and Pierre Gastinel, Ann. de dermat. et syph. **7**:97 (March) 1919.

Simon and Gastinel made serologic studies in ninety cases of primary syphilis. The Bordet-Wassermann technic and the method of Hecht were used in conjunction. The Hecht reaction was more constant, it appeared earlier, and lasted longer than the Bordet-Wassermann reaction; on the other hand, it is exposed to errors sometimes difficult to avoid, owing to the complex nature of its technic; it should therefore not be used alone, but in conjunction with the Bordet-Wassermann technic, thereby uniting the sensibility of the former with the precision of the latter.

Bechet, New York.

WASSERMANN REACTION AND MISCARRIAGES. Herman Goodman, Surg., Gynec. & Obstet. **30**:368 (April) 1920.

Eighty-seven per cent. of 1,320 pregnant women were negative to the Wassermann test. Only 6.7 per cent. gave a ++++ reaction, and in 2 per cent. the Wassermann was +++. Of the Wassermann negative multipara, 37 per cent. had suffered one or more miscarriages as compared to 52 per cent. of the ++++ cases. No ++++ Wassermann patient gave a history of having been pregnant more than six times. Only one woman among the 1,320 knew she was infected, although approximately one woman out of each eleven gave a strongly positive reaction.

Goodman, New York.

ANOMALOUS FORMS OF PAPULOPUSTULAR SYPHILIDS. Civatte, Ann. de dermat. et syph. **7**:123 (March). 1919.

The author reports two cases in which oval, more or less dark red, squamous, infiltrated plaques were found on the trunk and legs of the patients. On the edges of these plaques were isolated lesions covered wth a squamous scale or crust. Others were frankly pustular. The dimensions of the papules were 2 or 3 mm. On the shaft of the penis were discrete vesicopustules on a reddened, rounded base; they contained a drop of bright yellow pus, and were acneform in appearance.

Bechet, New York.

L'ECZEMA TUBERCULIDE (THE ECZEMATOID TUBERCULID). G. Milian, Paris méd. **10**:206, 1920.

The possibility of a tuberculous origin of many cases of eczema was called to Milian's attention by the case of a man who had two attacks of eczema, each coincident with an attack of pulmonary tuberculous marked by hemoptysis. Further observation has led him to believe that 80 per cent. of all cases of vesicular eczema are merely a symptom expressive of tuberculosis or, as he expresses it, "the syndrome of vesicular eczema is a tuberculide in 80 out of 100 cases." He states that every time he has searched for tuberculosis in an eczematous patient, he has found it; sometimes in an acute stage, but usually latent, sclerous, osseous, glandular, etc., in type—a general tuberculous soil.

Milian believes that a tuberculous microbic theory explains all the etiologic and clinical characteristics of vesicular eczema and its evolution, and he cites the association of the disease with tuberculids and true tuberculosis of the skin in support of his theory.

Senear, Chicago.

SEQUENCE AND ARRANGEMENT OF PALLOR AND REDNESS IN IRRITATED SKIN OF NORMAL AND DERMOGRAPHIC INDIVIDUALS. L. B. Bibb, Arch. Int. Med. **25**:680 (June) 1920.

Mechanical, chemical, thermal and electric means were employed in producing irritation on the skin of normal and dermographic persons with a striking similarity in the lesions produced as they all tended to wheal formation. The contact spot in practically all cases showed pallor immediately with a surrounding reddened zone within a few minutes.

He concludes from his experiments that the tissues studied tend to react in stereotyped manner to all the irritants investigated.

Jamieson, Detroit.

UEBER EINEN FALL VON IODODERMA TUBEROSUM (CASE OF IODERMA TUBEROSUM). Georg Tiefenbruner, Dermat. Ztschr. **29**:206 (April) 1920.

Following the taking of about twelve teaspoonful doses of potassium iodid (5 grains in a dose), a woman of 49, with a history of bladder trouble and with a chronic nephritis, presented the lesions of iodid dermatitis, which has been described as "ioderma tuberosum fungoides," "ioderma pemphigoides tuberobullosum" and "ioderma tuberosum." The face, especially the nose, the mucous surface of the hard palate and the extremities were the sites of the eruption, and one lesion was on the back, which is ordinarily free. New lesions appeared for a week after the iodid was discontinued.

The patient died. Necropsy showed, in addition to the lesions of the skin, a chronic nephritis with contraction, myocarditis, chronic bronchitis, edema of the brain and purulent otitis media (left).

Goodman, New York.

LE SYNDROME MALIN DANS LA SYPHILIS (THE MALIGNANT SYNDROME IN SYPHILIS). La Capére and Decrop, Paris méd. **10**: 203, 1920.

Struck by the great prevalence of malignant cutaneous syphilis among the native Arabs of the plains, La Capére and Decrop noticed that the natives of the mountain regions escaped these precocious lesions and were impressed with the fact that the distribution of malignant syphilis corresponded closely to the distribution of malaria. Studying along this line they found that the persons affected by malignant syphilis also had vascular hypotension. Anemia and asthenia, which apparently result from the particular malignancy of the infection, in reality account for it; they are manifestations primarily due to a pre-existing hypotension of which malaria is the principal cause among the Arabs.

Senear, Chicago.

BULLOUS ERUPTION COMPLICATING MEASLES. Frank C. Neff, Am. J. Dis. Child. **19**:469 (June) 1920.

The author reports an interesting case of an extensive bullous eruption complicating measles. The child, a girl, aged 6, developed a severe case. The temperature was 105; she had congestion of the eyes and a severe cough. Bullae began to appear in the first twenty-four hours of the measles eruption.

and rapidly covered the entire body. The measles eruption was no more pronounced than one sees in well marked cases, but the lesions persisted and the color became dusky and bluish.

The bullous eruption consisted of large bullae and some vesicles, but the most pronounced feature was the far reaching separation and maceration of most of the superficial layer of the skin, which resembled an extensive burn. The child died of the measles in collapse on the fifth day.

The author concludes that he had to deal here with a distinct exanthematous disease of the nature of pemphigus, complicating or secondary to the infection of measles.

OLIVER, Chicago.

ZUR FRAGE DER BLASENSYPHILIS (SYPHILIS OF THE BLADDER). C. POSNER, Dermat. Ztschr. **29**:193 (April) 1920.

In an effort to learn the incidence of bladder syphilis, the author undertook the routine cystoscopic examination of all his female syphilitic patients. Among the 135 reported in this paper, he notes that not one presented undoubted evidence of syphilis of this organ, although many of the women had bladder pathology due to an antecedent gonorrheal infection. He will report later his observations on the bladder of nonsyphilitic women in order to furnish material for comparison.

GOODMAN, New York.

A CASE OF BLUE CHROMIDROSIS. MARIO TOTTA, Arch. Rio-Grandenses Med. **1**:47, 1920.

The patient was a physician, aged 46, who had a neurotic temperament and had had several attacks of manic-depressive insanity. The abnormal perspiration was confined to the skin of the scrotum and the adjacent parts of the thighs, which appeared covered with blue moisture of a deep hue. There was no hyperidrosis. The chromidrosis was more marked when the patient was nervous or excited. The chemical analysis of the coloring matter found in this case proved it to be a ferric salt.

PARDO-CASTELLO, Havana.

THE TREATMENT OF SCABIES WITH AN ALCOHOLIC SOLUTION OF BETANAPHTHOL. SLOBOZIANO, Gaz. d. hôp., Feb. 3, 1920, p. 181.

Sloboziano employs the following formula: betanaphthol, 28 to 40 gm.; alcohol, 90 per cent., 400 gm. This suffices for one treatment. It is applied on the dry skin without rubbing or preceding baths. The entire surface of the body is moistened. On the scrotum the solution should be diluted. The applications are made twice a day for three or four days. The solution is well borne. The author did not observe any secondary dermatitis.

BECHET, New York.

THE DIAGNOSTIC VALUE OF LYMPHOCYTOSIS IN SYPHILIS. S. MAZZA and R. CORVALAN, Prensa Med. Argentina **4**:35, 341.

The authors made blood examinations in 250 cases of syphilis in its different stages. In all of them the cell count showed a slight lymphocytosis of 29.16 per cent. as an average, with extreme cases of 52 per cent. and 16.33

per cent. The authors have also verified that in many normal cases and in other diseases like chickenpox, smallpox, leprosy and malaria, a similar percentage in the lymphocyte count may be observed. They conclude that true lymphocytosis begins at or above 40 per cent., that the increase in lymphocytes observed in some cases of syphilis, is not constant and high enough to be considered of diagnostic value and that the percentage should never be based on a count of less than 300.

V. PARDO-CASTELLO, Havana.

LA DERMATOLOGIE ET LA SYPHILIS EN 1920 (DERMATOLOGY AND SYPHILIS IN 1920). DR. MILIAN, Paris méd. **10**:181 (March) 1920.

In a general review, Milian discusses, as among the most important contributions to the subject of syphilis, Levaditi and Moore's study of the treponema in general paralysis, Nicolau's work on the spinal fluid in the primary stage of syphilis, Simon and Gastenel's discussion of the evolution of the serologic reaction in the course of the chancre and various studies in the treatment of syphilis, the icterus following arsphenamin treatment and the so-called arsenical erythemas. In the dermatologic field are discussed Jeanselme's work in pediculosis, Darier's discussion of the parasitic nature of dyshidrosis, and Gougerot's attempt to classify the various forms of cutaneous infections.

SENEAR, Chicago.

THE CALCIUM CONTENT OF THE BLOOD WITH SPECIAL REFERENCE TO CANCER. OTTO KREHBIEL, J. Cancer Res. **5**:199 (April) 1920.

In cancer the average blood plasma calcium content was found to be within normal limits and no characteristic concentration accompanied any given type or location of neoplasm. The results were similar for benign tumors and for thromboangitis obliterans and low for severe nephritis, eclampsia and tetany. Thirty-four cases of malignant disease were studied, the calcium content varying from 5.8 to 15 mg. per 100 c.c., the average being 9.4 mg. Accepted normal figures are 9 to 11 mg.

H. R. FOERSTER, Milwaukee.

EIN FALL VON URTICARIA PERSTANS VERRUCOSA (CASE OF URTICARIA PERSTANS VERRUCOSA). HANS HIRSCH and WALTER BRUCK, Dermat. Ztschr. **29**:216 (April) 1920.

Under this title, Hirsh and Bruck describe a case of prurigo nodularis in a woman of 40 years, who for four years had presented an increasing number of pruritic nodules over the body. A photograph is given. The literature is reviewed with a bibliography.

GOODMAN, New York.

SUBLEUKEMIC ERYTHRODERMIA WITH PSEUDO CURE. A CAESAR and J. TAPIE, Ann. de dermat. et syph. **7**:114 (March) 1919.

This is a report of a case of lymphadenosis and erythrodermia with spontaneous remission of the symptoms, of several months' duration, previous to a fatal termination.

BECHET, New York.

UEBER DIE VANADIUM THERAPIE BEI SYPHILIS (VANADIUM THERAPY OF SYPHILIS). FERDINAND WINKLER, Dermat. Wchnschr. **70**:147 (March) 1920.

This article gives a review of the literature; nothing new.

ZIMMERMANN, Baltimore.

NOCHMALS EIN FALL VON SOGENANNTER DERMATITIS DYSMENORRHOICA SYMMETRICA BEIM MANNE (ANOTHER CASE OF SO-CALLED DERMATITIS DYSMENORRHOICA SYMMETRICA IN MAN). A. BRAUER, Dermat. Ztschr. **29**:211 (April) 1920.

This is part of a discussion concerning the identity of the so-called new dermatitis of Matzenauer and Polland.

UEBER DIE BERUECKSICHTIGUNG DER HAUT UND GESCHLECTSKRANHEITEN BEIM ZWANGSFAMULIEREN (CONSIDERATION OF SKIN AND VENEREAL DISEASES UNDER THE SYSTEM OF COMPULSORY CLINICAL CLERKSHIP). ERICH HOFFMANN, Dermat. Ztschr. **29**:214 (April) 1920.

This is a plea for a compulsory period of clinical instruction in skin and venereal diseases in the new curriculum. The proposal is made to include instruction in the social hygiene program (campaign against prostitution, sexual instruction), history taking and reporting.

GOODMAN, New York.

CONCERNING THE WASSERMANN REACTION AS THE THERAPEUTIC INDEX FOR SYPHILIS. BERNARD OETTINGER, Am. J. Syphilis **4**:297 (April) 1920.

In support of his view that the Wassermann reaction is not a reliable guide for treatment, the author points out those cases of late syphilis, particularly of the nervous system, which continuously react positively to the Wassermann after long continued intensive treatment and which may be done irreparable damage by such treatment. On the other hand, false security may be felt as a result of negative laboratory findings in definite syphilitic conditions.

TOMLINSON, Omaha.

UEBER POROKERATOSIS (POROKERATOSIS MIBELLI). W. BRUCK and H. HIRSCH, Dermat. Ztschr. **29**:223 (April) 1920.

A severe case of porokeratosis in a boy of 16 months is described. There is an exceptionally good review of the literature, histology, etiology and treatment of this dermatosis. They conclude that porokeratosis belongs to the nevus group of diseases. The bibliography is complete.

GOODMAN, New York.

A CASE OF MALIGNANT PUSTULE, IN WHICH THE INCUBATION PERIOD WAS KNOWN. H. J. MCCURRICH, Brit. M. J. **1**:828 (June 19) 1920.

The interesting features of this case were: The disease started from a razor cut. The patient knew the incubation period of the papule and vesicle.

The patient, a schoolmaster, aged 36, cut himself with a razor while shaving. He was using a new shaving brush for the first time. Thirty hours later he noticed a painful pimple at the site of the cut, and twelve hours later the papule had become a vesicle. The vesicle discharged, and two days later his neck became stiff and swollen. Three days later he consulted a physician, who excised the lesion and began the administration of antianthrax serum. The patient made an uneventful and rapid recovery.

Cultures from the pustule showed staphylococci and a few anthrax bacilli; a culture of the shaving brush showed *B. anthrax*, though a guinea-pig inoculated was apparently unaffected.

If the micro-organism on the shaving brush was anthrax, its virulence apparently was attenuated.

OLIVER, Chicago.

MANUFACTURE OF THE COOLIDGE ROENTGEN-RAY TUBE. R. C. ROBINSON and C. N. MOORE, Am. J. Roentgenol. **7**:224 (May) 1920.

A brief record of the manufacture of the two types of Coolidge tubes, with photographs of some of the machinery of the laboratory and factory of the General Electric Company.

GOODMAN, New York.

THE ROENTGEN-RAY TREATMENT OF ACNE VULGARIS. H. C. SEMON, Brit. M. J. **1**:700 (May 22) 1920.

In a well written article, the author concludes that while acne vulgaris in its early stages can be relieved in many ways by vaccines and the application of lotions and ointments containing sulphur, resorcin or mercury, a cure can only be attained by the judicious application of the roentgen rays.

The nodular and keloidal varieties of the disease are not amenable to relief or cure by any other method.

Relapses after apparent cure by roentgen rays are rare.

There are no permanent contra-indications to the treatment by roentgen rays; temporary cosmetic stigmas are sometimes encountered, but permanent disfigurement is the result of faulty technic.

OLIVER, Chicago.

LIPOMAS SUBCUTANEOS MULTIPLES (MULTIPLE SUBCUTANEOUS LIPOMAS). VICENTE GIMENO, Los Progr. de la Clin. **8**:268 (April 30) 1920.

Gimeno discusses the various types of subcutaneous lipomas that are ordinarily encountered, and gives a photographic clinical and microscopic study of an extensive case under his observation. His treatment was surgical, with the addition of the ingestion of thyroid extract, as good results have attended endocrine medication.

GOODMAN, New York.

SYPHILIS INSONTIUM. J. C. MCWALTER, Brit. M. J. **1**:827 (June 19) 1920.

It is generally taught that syphilis is transmitted to the fetus only at conception or in the earlier months of pregnancy. The case reported is one in which it appears conclusively that infection can take place in the eighth month of pregnancy.

The patient, a married woman in the early thirties, the mother of four healthy children, gave no history of abortion. She developed an ulcer at the angle of the mouth in which the *Spirochaeta pallida* was found—an evident chancre—and was immediately put on antisyphilitic treatment of mercury and iodids. The sore rapidly healed and in four weeks she was delivered of a healthy appearing infant. Five weeks later, the child developed unmistakable signs of congenital syphilis, which cleared up rapidly under syphilitic therapy.

OLIVER, Chicago.

RECURRENT IRITIS ASSOCIATED WITH DERMATITIS EXFOLIATIVA: REPORT OF A CASE. SANFORD GIFFORD, Am. J. Ophth. **3**:433 (June) 1920.

CATARACT PROBABLY DUE TO ROENTGEN-RAY EXPOSURE. OSCAR WILKINSON, Am. J. Ophth. **3**:435 (June) 1920.

The case reported is one of double simultaneous cataract in a woman 40 years of age, with negative history and findings, with the exception of a lupus erythematosus of the face. During a two and one-half year period this patient received more than sixty unfiltered roentgen-ray exposures to the face, during which the patient's eyes were uncovered and open. A simple cataract operation resulted successfully.

FOERSTER, Milwaukee.

LEUKODERMIA. W. KNOWSLEY SIBLEY, Proc. Roy. Soc. Med. **13**:71 (May) 1920.

An extensive case is reported. GUY, Pittsburgh.

CUTANEOUS SARCOID OF BOECK. A. M. H. GRAY, Proc. Roy. Soc. Med. **13**:63 (May) 1920.

A generalized eruption of lesions began as pinhead papules and attained the size of a sixpence piece; the well developed lesions were copper colored and of waxy appearance. Some showed definite hemorrhage on legs. When confluent, the patches became clear at the center and spread, leaving pigmented areas. Superficial ulceration was noted and considered to be of traumatic origin. There were from walnut to orange sized tumors on the bursae of elbows and knees. The lymphatic glands in the axillae and groin were enlarged. Section showed a granulomatous structure, with giant cells deep in the section; no organisms were found. There was definite improvement under novarsenobillon.

GUY, Pittsburgh.

CIRCINATE ERYTHEMA. E. G. GRAHAM LITTLE, Proc. Roy. Soc. Med. **13**:59 (May) 1920.

A more or less generalized eruption of erythematous lesions with distinctly raised edges (varying in size from a dime to palm of the hand), which enlarged by peripheral extension, was accompanied by factitious urticaria. The eruption had been for six months unaffected by teeth extraction and various local applications, but cleared markedly in four days under 20 grain doses of calcium lactate, three times a day.

GUY, Pittsburgh.

MORPHEA OF ACUTE ONSET. E. G. GRAHAM LITTLE, Proc. Roy. Soc. Med. **13**:59 (May) 1920.

A girl, aged 12, developed typical sclerodermatous patches in two weeks' time.

GUY, Pittsburgh.

ZUR NEOSALVARSANTHERAPIE BEI LUETISCHEN ERKRANKUNGEN DES HERZENS UND DER AORTA (NEOSALVARSAN IN THE TREATMENT OF SYPHILIS OF THE HEART AND AORTA). KUNO KOTHNY and ALBERT MÜLLER-DENHAM, Wien. klin. Wchnschr. **33**:77, 1920.

The authors report seven years' experience in treating syphilis of the heart and aorta with neosalvarsan. They are guided by the general condition of the patient in initiating the treatment and begin with the smallest doses (from 0.05 to 0.075 gram) at intervals of three or four days. The 0.3 gram dose is considered too large even as the maximum, and the authors have restricted themselves to 0.15 or 0.2 for largest doses. Mercury is utilized in the treatment. With a more intensive administration of the drug, Romberg reported that his patients lived an average of three and a half years after treatment was begun. With the smaller doses given by the authors, the average is between five and six years if treatment is continued.

GOODMAN, New York.

TRADE ECZEMA. W. J. O'DONOVAN, Proc. Roy. Soc. Med. **13**:75 (May) 1920.

One man had a dermatitis of the hands, arms and face produced by red oil, a dyestuff. The condition was treated with acetone, which is a dye solvent, and the eruption cleared in four days. The second patient used bismarck brown in the course of leather work. The eruption was a dermatitis of the hands, arms and face.

GUY, Pittsburgh.

DIE ANSTALT FUER KRAETZESCHNELLKUREN IM WILHELMINENSPITAL IN WIEN (INSTITUTION FOR RAPID TREATMENT OF SCABIES AT WILHELM HOSPITAL, VIENNA). FRANZ SCHÖNBAUER, Wien. klin. Wchnschr. **33**:105, 1920.

The equipment and the administrative organization of the hospital for intensive treatment of scabies is described. The advantages in bed space and in money are given, and it is stated that only by the institution of the three-hour cure can the pandemic of scabies be conquered.

GOODMAN, New York.

ANESTHETIC LEPROSY. E. G. GRAHAM LITTLE, Proc. Roy. Soc. Med. **13**:59 (May) 1920.

A Hindu medical man, shown before the section in 1915, had an eruption on the right leg which was diagnosed as probable lichen planus or tuberculosis. Recently a very complete anesthesia of the affected areas developed, but as yet Hansen's organism has not been found either in the tissue sections or in the nasal discharge.

GUY, Pittsburgh.

LUETISCHE TRACHEOOSOPHAGUSFISTELN (SYPHILITIC TRACHEO-ESOPHAGEAL FISTULAS). MAX KRASSNIGG, Wien klin. Wchnschr. **33**:130, 1920.

Fistula formation between the esophagus and the trachea is not rare, but syphilis is seldom mentioned as the cause of such fistulas. Krassnigg had the opportunity of studying a case from the stage of stricture to death, which was caused by an aspiration pneumonia despite antisyphilitic treatment. In cases reported in the literature, nutrition was maintained by gastrotomy and artificial feeding. Specific therapy of an existing fistula may increase it very quickly. Pneumonia usually ensues, however, and the patient dies.

GOODMAN, New York.

GENERALIZED RODENT ULCER. A. M. H. GRAY, Proc. Roy. Soc. Med. **13**:68 (May) 1920.

A man, aged 51, with a family history of psoriasis, had epitheliomas scattered over the entire body.

GUY, Pittsburgh.

THE INTERNAL TREATMENT OF PSORIASIS. R. SABORAUD, Presse méd. **28**:53 (Jan. 21) 1920.

Sabouraud reviews the various well-known dietetic and medicinal measures used in psoriasis. He has used the vaccine made by Danysz, from the microbic flora in the fecal matter of the subject, with occasional good results; but he states that as yet nothing has been found that has proved a specific in this usually rebellious affection.

BECHET, New York.

EXTENSIVE VASCULAR NEVUS. A. M. H. GRAY, Proc. Roy. Soc. Med. **13**:71 (May) 1920.

A port wine mark involved the entire body except the right front side of the chest.

GUY, Pittsburgh.

SYPHILIS AND PREGNANCY. WILLIAM JACKSON YOUNG, Surg., Gynec. & Obstet. **30**:508 (May) 1920.

Two hundred of 267 Wassermann examinations of pregnant women at the Louisville Public Hospital gave negative results. Fifty tests were either +++ or ++++, and seventeen were + or ++. Few of the women presented any cutaneous evidence of the disease.

GOODMAN, New York.

TAR CARCINOMA. J. H. SEQUEIRA, Proc. Roy. Soc. Med. **13**:73 (May) 1920.

Two cases of squamous cell carcinoma developing in men handling pitch are reported.

GUY, Pittsburgh.

Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

Regular Monthly Meeting, May 7, 1920

WILLIAM A. QUINN, M.D., *Presiding*

URTICARIA PIGMENTOSA. Presented by DRS. ORMSBY and MITCHELL.

In this patient, a woman, aged 34 years, the disorder had been present for five years, during which time the lesions had remained stationary. A biopsy had been performed but the mast cells usually found in urticaria pigmentosa were not present. The case was one of the acquired type. (For further description see the *Journal of Cutaneous Diseases* **36**:469, 1918.)

DISCUSSION

DR. NORMAN WALKER (by invitation) said he had not seen any cases of acquired urticaria pigmentosa. The cases he had seen had all been in children, but he saw very little difference between these adult cases and those in the children. Much stress was laid on the urticaria, whereas the pigmented lesion was the one of importance to the patient.

A CASE FOR DIAGNOSIS. Presented by DR. WAUGH.

An infant, aged 2 weeks, was of normal appearance at birth, but twenty-four hours afterward the skin became hard and contracted, both eyelids were markedly everted, the mouth was open, the child could not nurse and had a pale, yellowish, waxy appearance. Three or four days later numerous fine, whitish lines, not unlike scar tissue, developed. At no time was there any bullous eruption. The skin was not mottled. After about a week desquamation began and had continued to the present time. The mother had one other child, aged 4 years, living and well. There were two miscarriages between the birth of the latter child and of the patient. On the right foot was a small band of skin which retained about the same appearance that the entire body presented two days after birth; a similar condition persisted on most of the scalp. At the time of presentation the child could nurse in a normal way, looked well and was gaining. There were no palmar lesions and no eruption on the plantar surfaces, but the entire body and scalp were involved in the process.

DISCUSSION

DR. WILE did not feel that he could offer any diagnosis. He thought it a very extraordinary condition occurring at birth with an apparent sclerodactylia. Such changes might be due to syphilis. There was a history of two miscarriages; the child had the appearance of a cachectic new-born infant, such as was seen in syphilis, and the associated exfoliative dermatitis was suggestive of syphilis in the new-born. He had not seen a case with such marked sclerosis of the fingers and toes and his second thought was that the case belonged to the scleremias, a case of which was presented before the society a year or two ago by Dr. Lieberthal.

DR. ORMSBY said the part of the skin that was left on the baby, that which had not exfoliated, looked like collodion, and when the child was born it probably looked as if it were covered all over with collodion. It has been thought that that type of case belonged to the ichthyotic group, but it was proved by Bowen some years ago that that layer was the epitrichium which had not been cast off. The condition was supposed to be congenital ichthyosis, but it was not. He had seen only one other case just like this; in that case exfoliation began soon after birth but, unfortunately, the infant died of pneumonia at 3 weeks of age. He believed the case of this infant belonged in that group.

DR. LIEBERTHAL said that his case healed in about three months and the child was still living.

DR. NORMAN WALKER said he was glad to hear Dr. Ormsby depart from the theory of congenital ichthyosis, because he claimed that this should be done.

DR. WAUGH said the attending physician told him that the baby had a normal appearance as far as physical development was concerned, but it appeared exceedingly oily, and two days after birth the skin looked as though it had been painted with collodion. It seemed to him rather improbable that the child could be syphilitic. It was normal at birth but during the first week it could not nurse and the undernourished appearance was due to this. The mother's blood gave a negative Wassermann reaction.

DR. WILE thought that the exfoliation was really of secondary interest, the most interesting thing being the sclerosis of the extremities which he had seen simulated only in the sclerodermas. Furthermore, one could not disregard the syphilitic element because the child was normal at birth, because a baby might be normal at birth and develop syphilis a few weeks afterward.

DR. MCEWEN thought that since the child was improving constantly and the skin beneath the exfoliating material was practically normal the diagnosis of Dr. Ormsby was correct.

BROMODERMA. Presented by DR. SENEAR.

A child, aged 14 months, had pneumonia in April and was given cough medicine for two weeks. Five days after stopping this medicine the eruption began. The lesions were still forming, some fresh ones being present on the forehead.

DISCUSSION

DR. FOERSTER considered this a typical instance of bromoderma. An eruption of this degree of development and distribution is not infrequent in children who have had whooping cough and have been given patent medicines containing bromids.

DR. MCEWEN concurred in the diagnosis of bromoderma.

DR. NORMAN WALKER agreed with the diagnosis and thought it remarkable that all over the world bromids produce these eruptions in children, not only in the form of local lesions but also largely with respect to distribution. He was not accustomed to seeing such plump children for in the towns in the middle of England during the war the women went to work shortly after the baby was born and left the children in the care of some woman who might give them teething powders to keep them quiet. The mothers knew nothing of this and the doctor was informed that the baby had been given no medicine. Why was it that potassium bromid given to children everywhere

affected the same areas of the body? Dr. Walker thought this fact should be kept in mind when considering the distribution of lesions. Casts of bromoderma which he had shown in demonstrating the effects of medicines the composition of which was not known had more to do with convincing the committee of the importance of his work than had anything else.

Dr. Senear had been unable to ascertain how much medicine the child was given, but it was administered for a cough following pneumonia. He was interested to know what the cosmetic effect might be. In a similar case reported in New York after the eruption was stopped, judging from the description, the end-result was very bad, for practically every lesion left a bad scar. His experience with bromoderma was limited and he was interested to know what the outcome would be.

Dr. Ormsby stated that the cases he had seen in infants and children had cleared up without any scar formation. When bromoderma occurred on the leg below the knee in adults it left quite pronounced scarring, not unlike that seen in blastomycosis.

Dr. Norman Walker agreed that bromoderma in a child would disappear without scarring. Chronic bromoderma on the leg below the knee, especially in epileptic patients, left a scar so closely resembling syphilis that experts were often confused. He cited the case of a man who had taken enormous doses of bromid whom he was intending to present in his clinic, and a professor said it was a clear case of syphilis.

SYRINGOCYSTOMA. Presented by Dr. Lieberthal.

In a woman, aged 25, married, the mother of one healthy child, with no miscarriage, about nineteen years ago, after an attack of scarlet fever, pimples started to develop on the chest, and to a slighter degree on the abdomen, back and neck. These lesions had shown no changes whatever at any time and had caused no subjective symptoms. There was no increased perspiration in the affected places. The rest of the cutaneous surface was free. She received high-frequency treatment about seven years ago, without any beneficial results. The present affection consisted of yellowish and yellowish red nodules varying in size from that of a pin point to a split pea, mostly hemispherical, and with rounded or irregular borders. They were more numerous, larger, closely arranged and of red color on the upper part of the chest, while on the lower part of the chest, on the abdomen and back they were smaller and rather pale.

DISCUSSION

Dr. Irvine did not care to venture a diagnosis but had thought of a syringocystoma as one of the possibilities.

Dr. Zeisler agreed with the diagnosis of syringocystoma and considered it a parallel case with the one shown by Dr. Ormsby some years ago.

Dr. Senear agreed with the diagnosis but said that in one case seen recently with Dr. Pusey they were thrown off the track on account of the extent of the eruption. It occurred in sweeping lines, like a Christmas tree, and made almost a solid sheet, the lesions being very small. Some of the lesions were grouped in such a way as to present the appearance of a single lesion. The striking thing was that while for the most part the eruption was on the right side, the left side of the abdomen was involved, and a round area, with the umbilicus as its center, was entirely free. He had no explanation to offer for this.

DR. WAUGH was much interested because he had only seen one case previously that resembled this. The case shown by Dr. Ormsby several years ago had more extensive lesions, involving the arms, abdomen and thighs.

DR. LIEBERTHAL stated that he based the diagnosis of syringocystoma on the first appearance of the lesions in early childhood and continuation of these lesions without any change whatsoever. The result of a bioscopic examination would be reported later.

CASE FOR DIAGNOSIS. Presented by DRS. ORMSBY and MITCHELL.

A woman, aged 46, presented lesions which had first appeared on the face two years previously, and a year later on the posterior surfaces of the shoulders. None had disappeared. On the nose and on the cheeks were several dark red infiltrated plaques and nodules varying in size from a fingernail to a small coin, elevated from 1 to 2 mm. Over the shoulder posteriorly there was a palm-sized area of grouped and coalescing flat, pink papules and nodules, ranging in size from a match head to a small fingernail. A few smaller lesions were present on the upper arm. There were no subjective symptoms and the Wassermann reaction was negative.

DISCUSSION

DR. ZEISLER thought the lesions on the cheeks were suggestive of lupus erythematosus but those on the back did not fit in with this diagnosis.

DR. EISENSTAEDT said that his first impression was that the case resembled lupus erythematosus more closely than anything else, but he was not willing to give this as a definite diagnosis.

DR. WILE thought the picture was confusing because of the attempt to make a single condition out of two different things. He thought the lesions on the face were erythematous lupus and those on the back simple lichenification.

DR. FOERSTER agreed with Dr. Wile that the lesions on the face and on the trunk differed in character. He could not say what the lesions on the trunk were, but the lesions on the face suggested the condition of angiolupoid, as described by Pautrier and Brocq, which is probably related to the nodular types of sarcoid of Boeck. These authors describe the occurrence of small, discoid, bluish red or yellowish plaques, few in number, limited to the sides of the nose and adjacent portions of the cheek, and seen at times at the angle of the jaw. The lesions are slightly elevated, firm and smooth, and have as a characteristic feature small dilated vessels running over the surface. He would be interested to know the outcome in Dr. Ormsby's patient.

DR. LIEBERTHAL said that the patient had appeared in his office two weeks before and the diagnosis entered on her record was that offered by Dr. Wile. After examining the back he wanted to excise a piece for examination, and the patient said "next time," and he saw her no more.

DR. ORMSBY said that the patient came into the office two days before presentation and he presented her for diagnosis. He had the same impression that the others had of the case. Some of the lesions had the appearance of lupus erythematosus but some were too nodular. Some of the old nodular cases of lupus erythematosus had turned out to be sarcoid and this one might prove to be that disorder. He had demonstrated a case some years ago as lupus erythematosus which developed lesions of sarcoid. The lesions on the back were not sarcoid, but those on the face might prove to be that disorder.

ERYTHEMA MULTIFORME. Presented by Dr. Zeisler.

In a man, aged 20, first seen about one week before presentation, there was a history of an eruption in the mouth with rise in temperature and sore throat. Three or four days later erythematous patches appeared on the palms and backs of the hands, then on the lower extremities. They had cleared up considerably, but in the beginning they were typical of the erythema iris type of lesion. Conjunctival lesions were also present. The mouth and lips showed extensively eroded areas covered with a yellowish pseudomembrane which was very painful. Cultures and smears from the mouth lesions and the Wassermann reaction were negative. Salicylates had been administered.

DISCUSSION

Dr. Potthoff said this was a case of erythema multiforme with some of the lesions on the hands of iris type.

Drs. Stillians, Senear and Mackey agreed with this diagnosis.

Dr. Norman Walker said he thought that some of the friends with whom he had been associated in the past carried distribution to extreme lengths. In his opinion Sabouraud carried it a little too far and Dr. Smith taught his students almost exclusively on location, having devoted a large part of his life to the study and teaching of the external distribution of cutaneous lesions, though he devoted some time to the study of internal causes. Dr. Walker thought it was extraordinary that the iris lesions should always affect the hands and less often the feet, and why they selected the mouth. It was very remarkable that one should give a vaccine internally and have it produce a certain distribution. Here was a vaccine which selected certain definite areas. He considered "erythema iris" a very regrettable name; the lesions were not like a rainbow at all, but much more like a target. If one wished to depress a patient this could be done by telling him he was sure to have several other attacks. Dr. Walker thought the older books did not dwell enough on the distribution of the lesions of this disease in the mouth. He had seen cases a number of times which had been diagnosed as syphilis because of this involvement. The distribution interested him particularly. He saw many cases and was interested to know if anyone had any suggestion to offer as to whether there was a possible cause for these cases.

Dr. Lieberthal stated that in erythema multiforme the mouth was affected only in a small percentage of cases. The disease has, unquestionably, various causes. Sore throat may produce it and so may gastro-intestinal affections, while in some instances disturbances of these parts may be manifestations of the disease.

Dr. Zeisler stated that the diagnosis of syphilis had been made on this patient at Wesley Hospital, and mercury and iodids were started. He had recently had two cases of erythema multiforme at the Cook County Hospital with mucous membrane lesions. One cleared up very rapidly when a peritonsillar abscess was drained. Dr. Zeisler was under the impression that many of these cases originated from infection of the tonsils, possibly a streptococcus.

LICHEN PLANUS. Presented by Dr. Quinn.

A fireman, aged 24, presented an eruption over the arms and body that had been present for three months. The eruption started on the wrists and

gradually became generalized. Some scaling was present and at times severe itching was complained of. Occasionally vesicles were present, some of them hemorrhagic. While in military service he was recognized as a typhoid carrier and in July, 1919, while in service on the Mexican border, he was badly frightened.

DISCUSSION

DR. MICHELSON thought the case was one of lichen planus, and considered it interesting because of the arrangement of the lesions in rings.

DR. POTTHOFF agreed in the diagnosis of lichen planus and called attention to the fact that there was some pitting or scarring, probably due to some previous trouble on the skin.

DR. STILLIANS said he had hoped to present this patient at the previous meeting, but because of the fact that after the administration of ¾ grain of mercury salicylate the man developed a high temperature and broke out in vesicular eruption he did not return. The eruption was not very profuse but was widespread. He wished an opinion as to whether or not this could have been due to the salicylate.

DR. QUINN stated that the patient was severely shocked in July, 1919, but believed this was too long ago to account for the development of these lesions. He had observed the man for four weeks and the eruption had cleared up to a considerable extent.

DR. IRVINE said that he had under observation a case of lichen planus just as generalized as this but without the circinate lesions. This man was in the hospital for a number of weeks with shell shock but the lichen planus did not develop until a number of months after that.

A CASE FOR DIAGNOSIS. Presented by DR. STILLIANS.

A man, aged 56, was infected with syphilis twenty years ago. Seven or eight years ago the present lesions appeared on the arms, and one year ago on the face. The lesions consisted of nodules in the skin and beneath the skin of the extensor surfaces of both forearms. Some of them were bluish red, others were the color of the normal skin. In certain areas were groups of nodules which tended to become circinate. On the left cheek was a plaque about 1.5 cm. in diameter, glossy and waxy in appearance and moderately indurated. The Wassermann reaction was strongly positive and the patient exhibited dyspnea and severe anginal pain on exertion.

DISCUSSION

DR. SENEAR said the positive Wassermann reaction suggested syphilis and that was probably the proper diagnosis in spite of the lack of symmetry of late syphilis. At a distance there was a distinct tendency to a rather arciform distribution. He had also thought of the nodular tuberculous lesions of the hypoderm described by Wende, as well as of subcutaneous sarcoid.

DR. STILLIANS stated that he had hastened to present the man before the lesions cleared up, and had seen him for the first time that afternoon. He agreed with Dr. Senear that the case was probably an unusual one of nodular syphilis. There were some subcutaneous plaques without any change in color of the skin over them, and he thought of the possibility of an atypical subcutaneous sarcoid, such as was shown about a year ago.

ULCER OF THE GROIN. Presented by Drs. Ormsby and Mitchell.

A man, aged 24, presented a large ulcerating lesion situated in the groin, which closely resembled the old serpiginous chancroid. The lesion followed an injury; operative procedure had been employed without result. The ulcer was soft, presented well defined edges, and a slightly suppurating floor. The bridges and undermined areas usually seen in serpiginous chancroid were absent, but the edges presented a circinate outline. Cultures produced only ordinary pyogenic organisms. The histologic section was not characteristic, merely showing the picture of granuloma.

DISCUSSION

Dr. Wile thought the case probably belonged to the group which was discussed at the January meeting, when Dr. Grindon so ably presented the record of a number of cases of ulceration in the groin which he concluded belonged to three different types; (1) the neglected chancroidal ulcer, with or without the finding of the bacillus, in which there was a direct history of exposure and a chronic ulceration of the groin; (2) the group of ulcers frequently seen in the semitropics, a report of which was recently published in the Archives of Dermatology and Syphilology, the chronic ulcerations in the pudenda, the specific organism of which had been found by Dr. Goodman in Havana, and (3) the group in which it was possible to rule out the tropical bacillus and also that of Ducrey, in which there was a chronic ulcer of the groin, the chronic, low-grade ulceration resembling closely tuberculosis, at least in the clinical picture. Dr. Wile believed this was a case of the last type, and thought that significant in this case was the extent of the ulceration on the abdomen, away from the normal lymphatics. The few cases he had seen had yielded everything bacteriologically one wished to look for—staphylococcus, streptococcus—everything but the spirochete of syphilis. All of the cases were characterized by extreme chronicity and resistant to treatment. In this case Dr. Wile ventured the diagnosis of ulceration of the groin, phagedenic in type, of unknown etiology.

Dr. Norman Walker recalled seeing a similar case thirty years ago with Dr. Barber, who published the case under the title lupus serpiginosus. The case was extremely obstinate to cure and presented the same appearance as this one.

Dr. Ormsby said the only cases he had seen like this were observed at least twenty years ago, and at that time he saw what was called "serpiginous chancroid." Those cases had a lesion on the penis, then a bubo formed and from this ulcerating bubo the lesions developed. The case under discussion was similar except that in those cases there were bridges of tissue, which were not present in this instance. This patient had no chancroid preceding the ulcer and there was no venereal history. The section shown under the microscope was not characteristic, but revealed inflammatory reaction.

DERMATITIS HERPETIFORMIS. Presented by Dr. Oliver.

A man, aged 68, presented a disorder which had been present for nine months. The lesions began as vesicles, some remaining as such and others becoming bullous. There was considerable itching. The patient also had a large umbilical hernia. There was an eosinophilia of 8 per cent., and a white blood cell count of 8,200.

DISCUSSION

DR. MACKEY thought it was a case of dermatitis herpetiformis.

DR. IRVINE considered it dermatitis herpetiformis and he was interested to see the pustular lesion, as he had rarely encountered this type in the few cases he had seen. In most the urticarial base and the subsequent pigmentation were characteristic.

DR. MICHELSON was impressed with the absence of any itching or burning or any scratch marks.

DR. WILE wondered whether a diagnosis of pemphigus could not be sustained. He felt if we were to base a differential diagnosis of dermatitis herpetiformis on grouping alone a certain number of cases of pemphigus would go as dermatitis herpetiformis. He believed it was a case of true pemphigus.

DR. SENEAR had been of the opinion that the case was one of dermatitis herpetiformis, but there were only pustules as primary lesions and the others seemed to him to be the result of crusts. There was nothing that usually went to constitute the multiformity in dermatitis herpetiformis, and after listening to Dr. Wile's remarks he thought the diagnosis of pemphigus should be considered.

DR. EISENSTAEDT thought the diagnosis of true pemphigus might be established. He had noticed the things brought out by Dr. Wile.

DR. NORMAN WALKER thought after a single examination, the case should not be called dermatitis herpetiformis. The man had no itching, the distribution was not so much on the shoulders as was usually found in dermatitis herpetiformis and there was a striking absence of the pigmented rings usually seen. He would not care to register a diagnosis of dermatitis herpetiformis without further observation.

DR. OLIVER stated that he had first seen the patient four days previously. At that time some of the lesions were vesicular and later the lesions became bullous. The patient did have itching, although he said he did not, and continually asked for lotions to relieve the itching. He had thought of pemphigus but on the whole thought dermatitis herpetiformis should be considered more probable.

ULCERATING SYPHILODERM WITH NEPHRITIS. Presented by DRS. ORMSBY and MITCHELL.

A man, aged 24, with a negative history previous to the present disorder, had lesions which had been appearing, healing, disappearing and reappearing over a period of six years, and had attacked at various times the scalp, neck, face, upper and lower extremities and the trunk. At the time of presentation there were many scars and active lesions. The ulcers varied in size from that of a silver half-dollar to four times that size and were crust covered, many presenting a rupial appearance. The edges were well defined but only slightly indurated. The scars were smooth, white, thin, shining, slightly depressed, and occurred in patches made up of individual smaller lesions. The urine contained a large amount of albumin and casts, the latter being chiefly granular. The Wassermann reaction was negative.

DISCUSSION

DRS. IRVINE and POTTHOFF thought it was blastomycosis.

Dr. Zeisler said the lesions looked to him like blastomycosis, but Dr. Ormsby said no organisms had been found, so the case was probably one of tertiary syphilis.

Dr. Stillians thought it was blastomycosis but it might be an ecthymatous eruption in a man with lowered resistance.

Dr. Norman Walker said he had not had a great opportunity to see cases of blastomycosis, but the scars suggested syphilis rather than blastomycosis.

Dr. Quinn said that the first cases of blastomycosis he saw were seen with Drs. Hyde and Montgomery and they greatly resembled the scars of late syphilis.

Dr. Ormsby said the scars of blastomycosis were something like those of syphilis, but the entire scar in this case was made up of a group of smaller scars, which was typical of syphilis and not of blastomycosis. The man presented a superficial late syphiloderm of a type which used to be seen frequently, but was rarely seen now; a type, also, which was very resistant to treatment. He had seen such patients who had to be cared for for many months and kept in bed. The cases responded very slowly to the old methods of treatment. This man had improved considerably under arsphenamin; he had received five injections, the first only 0.2 gm., and the second 0.3 gm. Dr. Ormsby was not at all sure that the nephritis was syphilitic; if he were, he would be more heroic as to treatment. The patient had now been under observation for two days and he would be placed in the hospital and tested out. There was no doubt in his mind that the case was syphilis but the Wassermann reaction had always been negative.

Dr. Wile asked whether it had not been Dr. Ormsby's experience that cachectic individuals with severe syphilis frequently had negative Wassermann reactions. He had under his care at the present time a patient whose body was covered with scars of an extensive rupial syphilid and whose Wassermann reaction had uniformly been negative. Within the past year he had seen a second case in which an indubitable diagnosis of syphilis of a malignant type in a cachectic individual was maintained in spite of the absence of a positive Wassermann reaction. It seemed as if in these severe cases there was no reaction on the part of the patient to the infection and no antibodies were produced. It was not impossible that the albuminuria present in Dr. Ormsby's case was part of the syphilitic process. Early syphilitic nephritis is a fulminant type and characterized by enormous albuminuria; casts are not a striking feature of the urinary picture. Dr. Wile suggested that if the albumin content was very high it would be presumptive evidence that the nephritis was syphilitic. It must be remembered, however, that the more chronic type of nephritis can also occur associated with the later stages of syphilis.

Dr. Ormsby stated that the albuminuria was chronic but not excessive, and the casts were quite abundant. About four years ago they had a patient with about 75 per cent., by volume, albumin and within a short time his kidney condition cleared up, as well as the lesions of syphilis, following one injection. This man had received five injections and was improved.

Note.—(July 23, 1920.) A large amount of arsphenamin has been given since the patient was shown, with the result that many of the lesions have healed and the urine has become perfectly normal.

A CASE FOR DIAGNOSIS. Presented by Drs. Ormsby and Mitchell.

A man, aged 32 years, presented a lesion on the lip which had been present for about two months. At first it was an excoriation which developed a new growth and at the time of presentation it was a warty lesion, having changed its type considerably. There was no glandular enlargement.

DISCUSSION

Dr. Michelson believed it was a plain wart on the lip but that it was potentially malignant and should be treated as such.

Dr. Irvine thought that the facts that the lesion was only a few weeks old, and that it was much higher in the center than on the edge, were in favor of a common wart, but he agreed with Dr. Michelson that it should be treated as essentially malignant.

Dr. Ormsby stated that when the man was first seen in the clinic the lesion was much inflamed, and there was no suggestion of its being wart-like at that time, but it had just been painted with iodin. The crust had been removed. The question in his mind then was whether it was a beginning epithelioma or an infection of some sort with which he was not familiar, or a primary lesion of syphilis. His impression at present was that it was a beginning epithelioma. It had bled slightly when the crust was removed.

EPITHELIOMA. Presented by Dr. Zeisler.

A man, aged 60, first came under Dr. Zeisler's care in March, 1920, at which time he presented an ulcerated lesion on the back, about the size of the palm. The patient wore an artificial arm and the lesion began about five years ago at a point where the strap crossed the shoulder. Under radiotherapy it had cleared up markedly, and was now rapidly healing.

DISCUSSION

Dr. Oliver considered the lesion an epithelioma that was healing under treatment.

BLASTOMYCOSIS. Presented by Drs. Ormsby and Mitchell.

A man, aged 36, had suffered with this disorder for twenty years. He lived in a neighboring state and had been treated in various places during this period. The lesions were situated about the anal region, extending over the perineum, involving the scrotum, part of the penis and an area down either side on the surface commonly attacked with eczema marginatum. The lesions were papillomatous areas and scars and a few superficial ulcers. The obstinate career of the disorder and the pain were unusual features. Smears showing the micro-organisms were presented.

BLASTOMYCOSIS. Presented by Dr. Stillians.

In an Italian, chauffeur, aged 45, the disease began in the right arm in 1914, but there had been lesions on the face, back and scrotum since the onset. He had been treated with radiotherapy, neo-arsphenamin and iodids. At the time of presentation he showed scars on the right arm, face and back, the large scar on the back showing a recurrent patch of dermatitis of recent date.

A man, aged 40, presented lesions that had disappeared under arsphenamin and iodid treatment. The lesions had been present for eight months, beginning while the patient was at work in the stock yards. The first lesion appeared on the face under the left eye, spreading rapidly over the entire face, wrists and hands. One lesion was present on the chest. He had received iodid and copper sulphate, without distinct improvement. One injection of 0.6 gm. neo-arsphenamin had proved very beneficial. After a second dose the lesions almost disappeared. Three weeks before presentation they again showed signs of activity; another 0.6 gm. was administered and the lesions disappeared almost entirely. The blastomyces had been demonstrated.

Dr. Norman Walker thanked the members of the society for their courtesy in arranging the meeting so that he could attend, and stated that he had read the society reports with great interest in the past and would do so with added interest in the future. The spirit of camaraderie among the members was very pleasant and he was glad to have an opportunity of being present.

Book Review

SYPHILIS. A TREATISE ON ETIOLOGY, PATHOLOGY, DIAGNOSIS, PROGNOSIS, PROPHYLAXIS AND TREATMENTS. By HENRY H. HAZEN, A.B., M.D. Pp. 646. St. Louis: C. V. Mosby Co., 1919. Price, $7.00.

There is room at present for a treatise that summarizes our present knowledge of syphilis. The study of syphilis has been so intensive in these last few years, so much knowledge is accumulating, so many men who are entitled to be heard are expressing their views on moot points, that we need new synopses of the subject at short intervals, and that man does a service who gives us a good one. Hazen has done this service. He has given us, if not a *magnum opus*, a book that is worthy to be called a treatise on syphilis. The entire subject has been covered, and the work takes on an encyclopedic character from the fact that he has enlisted the cooperation of many authorities who have written on topics with which they are especially familiar.

To enumerate only the chief contributors: Reasoner has written on infection and immunity; Dunlap, on bones, joints, etc.; Fowler, on the male genitourinary organs; Lind, on the central nervous system; Dabney, on the eye; Greene, on the ear; Craig, on the Wassermann reaction, and Schamberg, on arsphenamin.

The work is well balanced, and does not fail, as so many works on syphilis fail, in being full on topics with which the author is familiar or interested, and weak on those with which he is not. Of course the large part of the work is by Hazen, and he has taken great pains to give the various topics in full, including the last word on the subjects.

Indeed, if there is a general criticism to be made of the book, it is that it is a syphilographer's book, a scholarly work; for it does not give the precise details and definite instructions about treatment, for instance, that the average physician—not only, the general practitioner but the average man in nearly all of the specialties—needs. But that is not a fair criticism, for what the average physician needs is to have pounded into him the elementary facts of our knowledge of syphilis. He needs a primer, and this is a treatise on syphilis.

The book can also be praised in detail. It is written in good style. The views are orthodox and sane, and restrained on matters of uncertainty. The author is courageous in just criticism, but liberal in his consideration of others' views. Altogether it is a commendable book. Illustrations are abundant. They are well selected and many of them of excellent quality. The printing, paper, and general make-up are first class.

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